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BRITISH MEDICAL JOURNAL

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HUMAN NUTRITION AND THE SOPHISTICATION OF FOODS AND FEEDING HABITS

SOME OBSERVATIONS, IMPLICATIONS, AND SPECULATIONS*

BY

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In the Constitution of the World Health Organization health has been defined as a state of complete physical, mental, and social well-being. Good nutrition undoubtedly contributes to the attainment of this state, so "food and health" would be a happier theme than "food and disease." Unfortunately, we are not so accustomed to measure healthiness as we are to recognize the signs of illness, so that for the most part the effects of food have been analysed in relation to evidences of ill-health and the occurrence of diseases.

Failure to feed properly—overfeeding, underfeeding, or taking a diet in which the proportion of nutrients is imbalanced—leads to primary malnutrition; nutritional disorders may also be secondary to infections and infestations (Platt, 1954a). Since these aspects of malnutrition are now familiar, I shall consider food and disease in a context which is perhaps not so well known and which may be of special interest to the general practitioner of medicine in the years to come.

SOPHISTICATION OF FOODS

Sir Edward Mellanby (1951), commenting on the increased incidence in the past fifty years of certain morbid conditions, said that he found it "difficult to avoid the conclusion that some at least of these increases in disease are due to errors in living recently introduced or greatly expanded in modern times," and that "it may be that one of these errors is the ingestion of food treated by unnatural chemical substances." In the past, chemical manipulation or, as I shall call it, sophistication of foods was, apart from gross adulteration amounting to fraud, largely concerned with preservation, but there is now a formidable array of chemical and other treatments for a variety of purposes; these provide "at least a subject worthy of inquiry" and one which "might well be considered whenever a disease commonly found in countries which use these methods has resisted all efforts of the investigator to find a satisfactory aetiological basis" (Mellanby, 1951).

Examples of the deliberate introduction of chemicals into food for human consumption and their accidental occurrence are included in the accompanying Table, which also gives references to some sources from which further information may be obtained. It will be clear, even from this limited bibliography, that the subject is so extensive that it will be possible here to make only brief comments on some selected aspects. These are dealt with in the same order as followed by the sections set out in the Table.

Unintentional Chemical Additives

The report of a Working Party on Toxic Chemicals in Agriculture and Residues in Foods (Ministry of Agriculture and Fisheries, 1953) contains a list of more than a hundred preparations, and these include some of the most powerful known poisons. The seriousness of the hazards to agricultural workers and others handling these aids to food production is recognized; but the Working Party, like a number of other authorities, reports that it has "been unable to discover any specific instances of illness which have resulted" from eating food treated with or exposed to some toxic chemical. "The position," it concludes, "does not therefore appear to have been *established*" (my italics) "as one of immediate danger." On the other hand, it does not consider that "it is one which allows of complacency."

I would be the last to deny the need for measures towards increasing crop production and preventing losses in storage, particularly in those parts of the world where food supplies are short. We have, however, to recognize in this, and indeed in the whole field of food technology, the possibility of a conflict of interests in which, as the *British Medical Journal* (1954) remarks, "It is doubtful if the influence of any such reformer [posing as a champion of the individual safety and protector of the public welfare] would ever equal or exceed that of a powerful commercial interest anxious to introduce a new material or technique into food production." The need for a strong and well-informed body of opinion is indeed well illustrated by an observation of the Working Party, commenting on the employment of bacterial rodenticides.

"The Public Health Laboratory Service and the Medical Research Council consider that the risks are such that the use of bacterial rodenticides should be discouraged with a view to their discontinuance. The Ministry of Agriculture's Infestation Control Division advise that immediate policy

*Based on a contribution to the Plenary Session on "Food and Disease" at the Annual Meeting of the British Medical Association, Glasgow, 1954.

should concentrate on ensuring proper care and attention in the preparation and use of these cultures and that any hasty action against these methods might lead to a serious dislocation in commercial rat destruction services." (Ministry of Agriculture and Fisheries, 1953.)

It is specially important to realize that much more is known about the hazards to health of these bacterial preparations than about many of the chemicals used in food whose presence may be difficult to detect and whose effects on the human body may be subtle, insidious, and long-delayed. The problem is not so difficult when, as in the case of D.D.T., evidence has been obtained of the effects of acute poisoning in man. It is much more difficult to decide whether the occurrence of D.D.T. in the milk of cows and in a number of staple foodstuffs treated with this insecticide may have insidious and possibly long-delayed effects on the human body (House of Representatives, 1952).

Illustrations of Various Treatments Employed at Different Stages in Food Production and Technology, with some Possible Hazards

Stage	Purpose	Agent or Treatment	Examples	Possible Hazards
Production	Increase of yield	Insecticides, fungicides, herbicides, rodenticides[1 2]	D.D.T.	? Residues in cows' milk and on foodstuffs[3 4 5]
			Organic phosphorus compounds—e.g., parathion[1]; thiourea; arsenic compounds	Toxic residues on fruit, skin-nerve poisoning[6]
			Salmonella rat bait[1]	? Bacterial food-poisoning[1]
		Antibiotics[7 8]	" Aureomycin " in chick foods	—
		Hormones[9]	Oestrogen implanted in cockerels	—
Processing	Enhanced acceptability	Refinement	Low extraction wheat-flour	Reduced dietary B-vitamin/calorie ratio[10]
			Highly milled rice	
			Sugar	
			Salt	—
		Addition of chemicals	Flour " improvers "	Manifested as fits in dogs fed on agenized bread[11]
			Colouring agents—e.g., dyestuffs	Carcinogenic action of butter yellow[12]
			Flavourings—e.g., artificial fruit essences	—
			Sweeteners—e.g., saccharin, dulcin, and P4000	Liver tumours with dulcin and kidney lesions with P4000 [13]
			Anti-oxidant[14], anti-browning, and anti-staling agents[15 16]	—
			Emulsifiers, fat extenders, and hardening agents (hydrogenation of oils and fats)	Renal calculus with polyoxyethylenemonostearate[4]
	Increased nutritive value (enrichment, fortification, ennoblement)	Addition of synthetic nutrients	Some B vitamins to refined cereal products[17 18]	Vitamin B imbalance[16 19]
			Ascorbic acid to fruit preparations[20]	—
			Ergosterol to margarine	—
			Amino-acids—e.g., lysine to cereals flours[21]	—
		Addition of mineral salts	Calcium carbonate and/or iron salts to wheat-flour[17]	Mineral imbalance[19]
			Iodides—iodates—to common salt[22]	—
			Fluorides to drinking-water[23]	—
		Addition of food concentrates	Fish-liver oil to margarine	—
			Skimmed-milk powder[24] and fish meal to bread[25]	—
			Yeast to various food preparations[26 27]	—
		Fermentation	Cheese	—
			Bread	—
			Many traditional preparations[28]—e.g., nuocmam[29]	—
	Preservation	Chemicals: Artificial	Benzoic acid, sulphur dioxides, and nitrites[30]	SO_2 destroys vitamin B_1, and sulphites cause haemorrhagic diathesis[31]
		Natural	Salt	—
			Sugar	Dietary imbalance
			Vinegar	—
		Physical means	Heating (including pasteurization)	Loss of some amino-acids by heating and in Maillard reaction[32 33 34 35]
			Drying	—
			Freezing	—
			Canning and bottling	—
	Cleansing of plant, equipment, and utensils	Detergents	Quaternary ammonium compounds[36]	Dermatitis[37]
Storage	Packaging and transport	Newly developed wrappings, etc.	Plasticizers[38]	See [38]
		Gas storage	For fruit, dried milk, and eggs	

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Intentional Additives

Many chemicals are added to foods in an attempt to satisfy the supposed desire of the consumer for uniformity of certain qualities of food products; for example, it is said that a large well-piled loaf of bread is demanded. Uniformity can be carried too far, and sometimes we have to deplore the success of the caterer in producing a sameness of taste whatever the dish. Those of us who are concerned with the application of the principles of nutrition do not want to conflict with the efforts of the food technologist and caterer; in fact, we believe that our interests are, or could be, in many respects identical, and often the methods of preparation of food by which the best flavours are secured are also those which retain or enhance the biological value of foodstuffs. The next section in the Table is concerned with increasing the nutritive values of foods by methods known as enrichment and fortification.

The fortification of foods is now a well-known procedure; however, the wisdom of removing a number of naturally occurring nutrients from wheat-flour and replacing them by a limited number of synthetic substances is open to question. It has been shown (Richards, 1945) that an animal given an imbalanced mixture of synthetic B vitamins may show no signs of deficiency, but if the animal bears young her offspring may show signs of deficiency of one of the factors which has not been restored to the mother's diet. When a dietary deficiency develops it would seem to be obvious that the diet should be improved—for example, by adding natural concentrates. In medicine, developments in bacteriology since Pasteur have been almost exclusively concerned with the study of micro-organisms pathogenic to man, but in food some micro-organisms may be not only non-pathogenic but actually beneficial to mankind. I would regret the passing of fermentative procedures, a natural way of improving the value of food which I have called "biological ennoblement" (Platt, 1946).

The conventional preservatives in current use are the successors of the spices of earlier days, which were used to disguise the flavours of food which had 'gone off"; some of these spices also had bacteriostatic or fungistatic properties. To-day the microbiologist is wisely directing his efforts towards eliminating the contamination of food products with pathogenic organisms so that chemical preservatives should not now be so necessary.

Chemical substances added to food may not only be toxic themselves but may also destroy, alter, or interfere with the absorption or utilization of nutrients, and the altered nutrients and their decomposition products are themselves sometimes harmful: for example, the effect on flour of agene is to convert the essential amino-acid methionine into a substance, methionine sulphoximine (Bentley *et al.*, 1950; Campbell *et al.*, 1951), which has a striking effect on the behaviour of some animals. This compound belongs to a fascinating group of substances known as anti-metabolites (Woolley, 1952).

Physical Treatment

As well as the problems associated with the addition of chemicals to food there are also problems which result from the physical treatment of foods by such methods as cooking, heating, drying, canning, and freezing (Lepovsky, 1953). Although, by definition, cooking is heating, the word does imply much more than this: its aim should be to retain or enhance flavours and to make the food appetizing and palatable. It is well known that flavours and food values are lost when the art of cooking is lost; in particular, the loss of ascorbic acid has been thoroughly examined (Stewart, 1946). In some respects the retention of ascorbic acid is a guide to good cooking, as flavours, colouring agents, etc., are dependent on the presence of chemical substances which, like this vitamin, may be leached out or destroyed in the course of many cooking methods.

It has been known for some years that fats and oils decompose on heating, fortunately at temperatures which are high compared with those normally employed in cooking, and that carcinogens are produced (Peacock *et al.*, 1953). The phenomena of denaturation of proteins and the "browning" or Maillard reaction between proteins and carbohydrates have also been familiar to biochemists for many years; they have now been associated with the lowering of the biological value of protein; there is evidence that in these changes the essential amino-acids lysine and methionine may be destroyed. With the rapidly increasing interest in protein malnutrition (*British Medical Journal*, 1952) which is now known to be prevalent in so many parts of the world these effects are likely to receive increasing attention. Are there any reasons for believing that they are relevant to unsolved problems in medicine in this country?

Lysine we know to be required for growth and for maintaining a normal blood picture; methionine and the other sulphur-containing amino-acid, cystine, are important in the nutrition of skin and hair (Platt, 1953). A relative methionine deficiency has been shown (Mann *et al.*, 1953) to be in monkeys a factor in the production of hypercholesterolaemia and atherosclerosis. The aetiology of a number of disorders of the blood, skin, blood vessels, and eyes is still in question; a case might be made out for investigating these in relation to recent developments in food technology. I want to stress the point that there may not necessarily be merely deficiency of a nutrient following destruction during some process, but this insufficiency may be combined with the effects of the altered nutrients behaving, for example, like the anti-metabolites.

Technical Difficulties

Attempts to assess the effects on the consumer of all these procedures raise great technical difficulties. Barnes (1951) states that "any substance added to food must display no demonstrable toxicity for animals and must satisfy rigorous standards of purity," but this toxicologist concludes that "the problem of the adulteration of food by chemical substances will come to lie within the field of nutrition rather than in the more strictly limited one of toxicology." It is difficult to reconcile with this the views of a pharmacologist who, for reasons which are by no means clear, would exclude nutritional and palatability effects from those used in determining an effective dose level, though he concedes that "it seems advisable that the effect of food additives on the nutritional value of the diet should be known" (Frazer, 1953). Animal experiments may afford some help, but we must face the conclusion that "it is impossible to conceive of animal experiments which will provide complete information about the toxic effects of chemicals on human beings" (Barnes, 1951). The demonstration by experimental or other techniques of the dangers to human health of a procedure introduced into food technology may follow its introduction only after a long lag period. We may note here that agene was in use in the flour-milling industry for 30 years before its toxic effects, even in animals, were recognized and explained.

If there are hazards, then I consider that they may be relatively greater if exposure occurs during the period when biochemical changes are most intense—that is, during growth; and the clinical results may appear only with advancing age. As in industrial medicine, so in food technology, each new development may raise new medical problems. The onus of assessment of hazards to the health of the consumer must be accepted by the medical profession, which must lose no opportunity to obtain, scrutinize, and weigh the evidence before countenancing existing practices in food technology and sanctioning new developments in this field.

SOPHISTICATION OF FOODS AND FEEDING HABITS

Changes have occurred and others are still occurring which affect the foods and feeding habits of mankind; prominent in the dietary history of this country are the results of the introduction of potatoes and, earlier still, the

change in the meat supply consequent on the provision of root crops for livestock. Alternating periods of shortage and comparative plenty, markedly seasonal variations in the diet, and very localized peculiarities of taste and custom are still to be found in many primitive communities. In sophisticated communities feeding now is generally characterized by an evenness of supply throughout the year and a uniformity of diet amounting often to monotony; this has been the result of advances in agriculture, food technology, and modern methods of transport. The health of the community may be affected, for better or for worse, to the extent to which these developments affect the predominating foodstuffs and influence feeding habits. I shall now discuss only one such development—the artificial feeding of infants with some form of cows' milk.

Infant Feeding

Two centuries ago, in this country, breast-feeding by the mother or wet-nurse was almost universal and was probably continued for two or even three or more years, as it still is in many parts of the world to-day (Platt, 1954b). In Western countries nowadays, however, the child is often artificially fed from its earliest days or is weaned from the breast at 6 to 9 months of age. It must be admitted that until quite recently there has been no very convincing evidence for the superiority of human milk to cows' milk (Platt and Moncrieff, 1947), and the preference for the feeding of human infants at the breast instead of with cows' milk has been almost entirely a matter of faith. Such differences as a calcium content five to six times greater in cows' milk than in human milk have been overlooked. However, the curves showing the relation between the calcium content of the infant and the duration of feeding on cows' milk and human milk are reminiscent of those mentioned below relating nitrogen content of the body to age. After six to ten months' feeding on cows' milk the proportion of calcium in the infant's body is more than half as much again as that in the infant fed on human milk (Stearns, 1939).

The fact that so few infants show gross clinical, pathological, and biochemical changes in the early months of life is a comment on the point made below about the differences that are likely to occur between individuals; there are here, however, grounds for apprehension about the possible delayed effects of excessive intake of calcium in artificial feeding. It has been stated (*Lancet*, 1954) that hypercalcaemia "must be quite a common disorder, for 42 cases have been reported in this country alone in the last year and many more have been recognized." The frequency with which a history of feeding on cows' milk is reported suggests that the practice is an important if not a determining factor in the causation of the condition.

I want now to offer some observations which have led me to speculate about the possibility that modern infant-feeding practices may be concerned in the causation of certain diseases which we associate with modern conditions of life and living, and for the occurrence of which we have as yet no satisfactory explanation. I have found (Platt, 1954c, 1954d) that milk in the infant rat's stomach separates into curds and whey. The curds, which are laid down in successive layers, are slowly digested and normally do not leave the stomach for 15 hours or more. The whey, however, leaves rapidly, and the greater part of it passes through the pylorus in 30 to 40 minutes. The casein of the curds appears to be broken down into its constituent amino-acids, but there are some grounds for believing that the components of the whey not only behave differently in the stomach, but may not be completely broken down before absorption. We do not know if milk behaves in a similar way in the human baby's stomach; indeed, very little appears to be known about this subject. It is customary, in the study of gastric function, to start by ensuring that the stomach is empty. If the infant animal takes milk into a stomach which has been empty for some time, an undifferentiated clot forms which contains pockets of air and mucus, and only after several hours is the usual pattern of layers restored. I suspect (Platt, 1954b) that there may be physiological as well as psychological grounds for a return to the recently reinstated system of feeding "on demand."

Since 1892 it has been known from Ehrlich's work on mice (Ehrlich, 1892) that antibodies can be transmitted in colostrum or milk from mother to offspring. Similar observations on the transference of immunity factors have been made on calves (Howe, 1921; Orcutt and Howe, 1922; Smith and Little, 1922), and these have been confirmed by electrophoretic methods for the pig (Foster *et al.*, 1951) as well as for the calf (Smith, 1948). The low serum cholinesterase of newborn puppies has been shown to be increased (McCance *et al.*, 1949) when they were fed on bitches' milk containing this enzyme, but not when they were fed on cows' milk or human milk. There is also an interesting observation made by Rutman (1950) on rats; he found that the infants of one strain, in which a poor ability to incorporate methionine into protein was demonstrated, acquired this ability when fed by mothers which had an efficient capacity for this process; presumably this was acquired by transference of some factor in the foster-mother's milk.

The importance of the protein components of colostrum and early milk may not be so great for the human infant as it appears to be for many species of animals. However, on the basis of the evidence available, I have wondered whether we should regard the mother during lactation not merely as a provider of food but also as a supplier of substances ready made for use by the infant until such time as he can synthesize them for himself. Is breast-feeding, therefore, a device by which provision is made for a transition between complete dependence on the mother before birth and complete independence after weaning from the breast?

Galactose and Myelination

A main component of whey is milk sugar—lactose—which is entirely contained in the whey. It is a disaccharide which is made up of glucose and galactose. As well as being present in milk as lactose, which is in part combined with neuraminic acid (Trucco and Caputto, 1954; Heyworth and Bacon, 1954), galactose is known to be a component of several substances found in the mammalian body. It is found in the cerebrosides of the central nervous system and in mucopolysaccharides in connective tissue (references to the occurrence of these are given below), in a galactan (Wolfrom *et al.*, 1947; Wolfrom *et al.*, 1952), and in the protein-bound carbohydrates of seromucoid, certain serum globulins (glycoproteins), and the carbohydrate of chorionic gonadotropin (Werner and Odin, 1949). We do not know if the human infant is able, in his early life, to synthesize galactose; indeed, we do not know if galactose can be synthesized in any human tissue at any age except in the mammary gland (Reiss and Barry, 1953). Galactose, therefore, may be a substance for which the human infant is dependent on his food—that is, in this case it would be an "essential" nutrient in the sense that some amino-acids and the accessory food factors are "essential" and the origin of any galactose laid down in later life is quite obscure.

The cerebrosides are the principal lipids of myelin, most of which, as is well known, is laid down after birth (Johnson *et al.*, 1949). Myelination continues until perhaps the fifth to sixth year of life (Kennard, 1952), and the progress of myelination of nerves may well be determined by the activity of the muscles with which they are connected. In this connexion I wish to draw attention to an observation (Stearns, 1939) the significance of which has not, so far as I know, been explained. This is that an infant fed on cows' milk stores nitrogen at a much greater rate than one on breast milk, and that at 6 months of age the percentage of nitrogen in the bodies of infants fed on cows' milk is about twice that in the bodies of those fed on human milk. Presumably most of this nitrogen is stored as muscle protein, and we may infer that in the cows'-milk-fed infant the rate of muscle development may be more rapid than in the breast-fed infant. If this also entails more rapid myelination of the appropriate nerves, and if the galactose for the

synthesis of myelin must come ready synthesized from the food, we have to take account of the fact that the cows'-milk-fed baby gets only two-thirds of the amount of lactose which he would receive if he were being fed the corresponding amount of human breast milk. Does this possible extra demand, coupled with the reduced supply of galactose, have any adverse effect on the subsequent health of the individual?

We know that when unusually large quantities of cerebrosides are synthesized, as in Gaucher's disease, those from the spleen and from the brain may contain glucose (Woolf, 1954). There was a report last year (Montreuil *et al.*, 1953) that glucose occurs along with galactose in the cerebroside of normal brain. It has been reported that in mammals there is a positive correlation between the percentage of lactose in the milk of the species and the cerebroside content of the brain (Brody and Sadhu, 1947). On feeding dextrose to young pigeons, glucocerebrosides were found to constitute one-third of the total cerebrosides, there being none in the brain of the normal birds (Sadhu, 1953a). Changes in the proportion of cerebroside to other lipids have been observed when weanling rats are fed whole milk as compared with skimmed milk (Sadhu, 1953b). It would seem from these observations that an investigation of the composition of the cerebroside of myelin of the human infant's nervous system should be made with a view to determining whether the substitution of cows' milk for human milk has any effect on it. I suspect that the effect on the composition of myelin may be particularly profound when an infant is artificially fed on a "humanized" cows' milk preparation which may supply as little as one-third of the lactose obtainable from human milk.

If glycocerebroside occurs as a substitute for part of the galactocerebroside, does it persist into adult life? We do not know the answer to this question. It might at first be thought, in view of the dynamic equilibrium of substances in the human body, that glucose would ultimately be replaced by galactose. This would depend on whether galactose could be synthesized in the brain or elsewhere in the body, and, if outside the central nervous system, could it pass through the haemocephalic barrier, which seems to be more difficult to cross in the mature than in the growing subject (King, 1939)? There is some evidence from isotope studies that metabolically the brain is somewhat isolated from the rest of the body. Thus there appears to be no significant turnover of C^{14} in rat-brain protein after the isotope has been incorporated in the organ during its period of growth (Schubert and Armstrong, 1949), and the general conclusion has been expressed that "there seems to be in the brain a degree of spatial permanency" (Folch-Pi, 1951). It may then be that, like proteins, the brain lipids remain throughout adult life within the brain metabolic pool.

Possible Consequences of Imperfect Myelination

If abnormal cerebrosides occur and persist, do they have any adverse effect on the subsequent health of the individual? In my contribution to the symposium on Food and Disease (Platt, 1954e) I contented myself with asking whether, if the composition of myelin is affected as a result of the sophistication of a feeding habit, this might have some possible relation to the prevalence of disseminated sclerosis. I shall now, so far as I am able, discuss this possibility in more detail.

Lumsden (1951) suggests two alternative views of the causation of disseminated sclerosis, one of them being that it is "a specific form of reaction on the part of the nervous system peculiar to certain individuals and, within limits, independent of its immediate precipitating cause." May the presence of an abnormal cerebroside determine the occurrence of this specific form of reaction? If this were so, it would fit in with a restatement of the meaning of the haunting term "abiotrophy" introduced by Sir William Gowers and defined as a primary nervous system disorder in which local tissue resistance is overcome, with consequent disintegration of that tissue. In a recent study of a familial myelinating disease it has, however, been stated that "there is more than suspicious evidence that the term primary is misleading, and that actually one deals with a primary disorder of metabolism with a secondary nervous system disorder" (Stadler *et al.*, 1954). There is, it seems, an important and relevant conclusion to be drawn from the study of the pathology of disseminated sclerosis—namely, that "some property of myelin determines the localization of the pathology" (Adams and Kubik, 1952).

If a poor supply of galactose in the infant's diet contributes to this specific form of reaction, then it might well be expected that disseminated sclerosis might be even more common than it is. There are, however, two possible considerations which might account for a comparatively low incidence: (*a*) the occurrence of the postulated "immediate precipitating factors," and (*b*) individual differences in rates of development of muscle and nervous system. Lumsden offers the hypothesis that, whatever the precipitating factors may be, the pathological changes may result from the action of a myelinolytic ferment; could it be that this is a cerebrosidase and that the glycocerebrosides may be more readily hydrolysed than the normal compound, or that there is no anti-enzyme for this reaction? These points are now being investigated.

So far as development of muscular and nervous systems is concerned there is now good evidence of quite remarkable differences in the ages at which various behaviour patterns are seen in infants (McGraw, 1943). How far these are associated with differences in the extent of myelination does not appear to be known, nor does there seem to have been any investigation of the possible relationships between the methods of feeding infants and their rates of maturation. There is evidence that there are differences for certain forms of behaviour up to 3 to 4 years of age (McGraw, 1943), that myelination may not be complete till 5 to 6 years of age (Kennard, 1952), and that breast-feeding is uncommon nowadays beyond 1 year.

Douglas (1950), in a survey in the United Kingdom, found, out of over 40,000 infants, only nine who were breast-fed up to 2 years of age. If the amount of galactose supplied to the infant is crucial then obviously the amount of breast milk taken, the duration of breast-feeding, and the amount of galactose obtainable from other dietary sources are all important. Materials containing galactose are known to come from plant sources (Black and Cornhill, 1954), but there is no evidence that they are assimilated; galactose-containing substances are also found in snails and slugs, and it is known that small "dew slugs" were at one time recommended for the nourishment of backward children (Hartley, 1954). In communities where breast-feeding is usual, and is continued for two to three years, disseminated sclerosis is rare and the cases reported are often unconfirmed by pathological evidence. Also, in other communities where feeding with carbohydrates, including cane sugar, is common in infancy—for example, in the West Indies—a syndrome with the features of a transverse myelitis is not uncommon and is suspected to be of nutritional origin. Inquiries are being made about the precise nature of this condition.

Dietary Damage in the Young

There may be some difficulty in accepting the hypothesis of a dietary defect in infancy resulting in a disease whose earliest clinical manifestations may be delayed till the second decade in life, or later. It is, however, being increasingly recognized that dietary damage in the young—or even prenatally (Giroud, 1954)—may have effects only late in life. Acute choline deficiency in the young rat may result in hypertension, but only in later life (Hartroft and Best, 1949) and after a period equivalent in man to about 20 years. Similarly, the development in a strain of mice of a type of arthritic degeneration occurring in older animals has been shown (Silberberg and Silberberg, 1952) to be strikingly affected by the nature of the diet throughout life. There is a good deal of evidence of the occurrence of a lag between a biochemical disturbance and the appearance of

pathological and clinical manifestations: one of the longest intervals is that recorded (Henry, 1946) in the development of epitheliomata of the scrotum and penis many years after exposure to the carcinogenic agent.

Most of the evidence that disorders in early life may produce tissue changes at an advanced age is derived from observations on animals, and, whilst it may be misleading to apply inferences from experiments in animals to the explanation of disease processes in man, it is obviously convenient to study such changes in animals with a short life-span. In the human species the period of growth is uniquely long in proportion to the life-span (Brody and Ragsdale, 1922–3), and in the study of human disease, therefore, we must be particularly concerned about disturbances during growth, neonatal as well as post-natal, and be on the look-out for sequelae in the adult. Thus the possible effects of artificial feeding of infants may not be seen for many years, and perhaps only after the tissues have been exposed to stresses or the effects of noxious agents. We may indeed be reaping in medical practice and in the post-mortem room to-day the results of methods of feeding infants and young children which were prevalent 20 to 30 years ago.

A conclusion about disseminated sclerosis on which there seems to be agreement is that "the major histopathologic changes seem to conform to those seen in degenerative diseases of the central nervous system" (Davison, 1950). The phylogenetically newer systems—the pyramidal tracts and the proprioceptive system—commonly suffer permanent damage (Martin and Elkington, 1946). These observations are of interest, since presumably the maturation of the neuromuscular mechanisms of the older systems is completed early in infancy; the swimming behaviour of the newborn infant, one of the oldest phylogenetic functions (McGraw, 1943), disappears in most infants in the first few weeks of life. Many disorders of nutrition and metabolism have clinical features in common with those of old age; and it has been stated that during "the involutionary period, the individual loses his capacity for homoeostasis as if involution were a mirror image of adolescence with senescence as a return to the physiological instability of infancy" (Frank, 1946). It might be, though I am not sufficiently well informed to do more than make the suggestion, that in the clinical signs of disseminated sclerosis may be found the mirror image of development, but as reflections which are revealed early and distorted as a result of imperfect myelination.

"Collagen Diseases"

Galactose is, as mentioned above, a constituent of some components of extracellular material (ground substance) and connective tissue. There has in the past been an almost exclusive interest in the biochemistry, physiology, and pathology of the cell, and until recently little consideration has been given to the nature and functions of the extracellular structures and substances. The concept of an "extracellular space" is being replaced and some of the properties hitherto attributed to the membrane of the cell are being ascribed to the extracellular matrix. One suggestion made recently is that the blood–brain barrier may be due to the existence of ground substance (Woollam and Millen, 1954).

The possibility that galactose might be a constituent of the mucopolysaccharides of the cornea was suggested by Suzuki (1939) and confirmed recently by Woodin (1952) and Meyer *et al.* (1953); its presence in connective tissue (Consden *et al.*, 1953) and in human subcutaneous tissue (Consden and Bird, 1954) has now been established. Several times has the presence of galactose in collagenous material been reported, and Glegg *et al.* (1953), who review these observations, have evidence that it is the reticular fibres of connective tissue which appear to have the sugars galactose, glucose, and mannose as integral constituents. During some work on wound healing Penney and Balfour (1949), in my unit, demonstrated the importance of mucopolysaccharides in skin for healing, and they associated this substance with the formation of reticulin fibres, an observation which is supported by the recent demonstration of Glegg *et al.* (1953) on the composition of these fibres.

Interest is growing in a group of disorders of connective or mesenchymal tissue which have been called "collagen diseases," and Robb-Smith (1952) has claimed that there is quite a lot of evidence that the mechanisms of formation of abnormal glycoprotein are associated with the morphogenesis of these diseases. I want to do no more here than to suggest that the supply of galactose—or substitution of glucose for this sugar—in the feeding of the infant and young child may affect the nature, composition, and reaction to stress in later life of the extracellular matrix and connective tissue, and may thus be a factor in the occurrence of a number of diseases which might be identified with the sophistication of living. I would add to Mellanby's suggestion, quoted at the beginning of this paper, a plea for a study of the effects of changes in feeding habits consequent on the various methods of sophistication of foods, and conclude with the support of a pathologist (Robb-Smith, 1952) that "yet more profit may be gained by considering the biochemical morphogenesis of which something is known and more can be learnt than by restricting oneself to aetiology of which almost nothing is known."

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TREATMENT OF SCHISTOSOMIASIS WITH "NILODIN"

BY

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A mine medical officer in the Union of South Africa has undeniable advantages in assessing the effects of treatment of schistosomiasis. In the first place, the mines of the Witwatersrand and Orange Free State are situated in "clean" areas, whereas the labour force is to a large extent drawn from heavily infested areas; therefore once the disease has been successfully treated the question of reinfection is not likely to arise to cloud the issue. In the second place, a wholly adequate follow-up of cases is possible, as natives recruited from the infested areas do not sign labour contracts for periods of less than nine months, and furthermore any mine employee can be recalled for re-examination at any time. Thirdly, a very large percentage of the tropical labour force, especially the Portuguese East African contingent, is infected with both *Schistosoma haematobium* and *S. mansoni*, so that an adequate number of cases are available for treatment and assessment.

At the Brakpan Mines in the Transvaal a trial was made of the use of "nilodin" brand of lucanthone hydrochloride (1-β-diethyl-aminoethylamino-4-methylthioxanthone hydrochloride; "miracil D") in the treatment of both urinary and rectal schistosomiasis. In the former the infecting organism was *S. haematobium*, and in the latter *S. mansoni*. In reporting the results certain aspects, such as the clinical diagnosis, presenting symptoms, tribal incidence, and haematology, have been omitted for the sake of brevity.

In both forms of infection the diagnosis was based on laboratory examination of specimens of urine and faeces respectively for the presence of viable ova. Ova are considered to be viable if free-swimming miracidia are present or there are active movements of miracidia within the ova. Occasionally an ovum remains motionless after exposure to water in high dilution, but the flame cells can be observed beating in the organism and the cilia may be moving. An ovum with none of the above signs but morphologically normal is referred to throughout this paper as "inert." After treatment ova are passed which can be referred to only as "macerated." They contain an amorphous mass; no movement or "pulse" of flame cells can be observed. Some ova are shrunken, while others appear to have swollen and burst. It is common to observe "globules" within macerated ova which are not seen in normal ova.

The nilodin used throughout the trial was in the form of tablets each of which contained 200 mg. In these circumstances it was usually impossible to adhere strictly to a particular scheme of dosage based on body weight. No patient was started on less than the specification decided upon, and when part of a tablet was indicated a whole tablet was given. Thus when the dosage was 20 mg. per kg. of body weight a day, a patient weighing 56.5 kg. would actually receive six tablets=1,200 mg. daily instead of the 1,130 mg. indicated by his weight.

URINARY SCHISTOSOMIASIS

Results of treatment in a total of 46 cases of infection with *S. haematobium* are presented. These are divided into two series in which the dosage, the course of treatment, the method of follow-up, and the method of urine collection differed.

Series 1

This series originally consisted of 37 cases, but 13 of these were excluded from the investigation for various reasons: in 9 cases the follow-up was inadequate, 3 proved to be cases of rectal schistosomiasis, and in the other case no viable ova were demonstrable before treatment. The remaining 24 cases were followed up for at least three months. Cases were re-examined once a week for the first three months and thereafter at monthly intervals.

Laboratory Examination

In most of these cases viable ova or miracidia were found in the first (casual) specimen of urine passed. In no case were more than three specimens required to make a positive diagnosis. The technique of urine examination used for both diagnostic and follow-up purposes is as follows.

The conical glasses of urine are allowed to stand for a variable period after collection, but not less than 15 minutes. The supernatant urine is then decanted; the remainder is well stirred, poured into a centrifuge tube, and spun down at 3,000 r.p.m. for three minutes. The supernatant urine is now discarded, and the centrifuge tube filled with tap water and again spun down. The supernatant water is discarded and the sediment shaken up in the few drops remaining. With a clean pipette in every instance the remaining drops are placed on a slide and examined. The search for ova can be made very satisfactorily with the low-power objective of the microscope, but to establish viability of an ovum the high-power lens (×800) is required. It is of the greatest importance that the complete sediment—that is, four drops as a rule—be examined at every re-examination. Each centrifuge tube as used contains 14 ml. of urine.

The great advantage of this technique for follow-up purposes is that the viability of ova can be established almost at once, it being common to find miracidia swimming in the drops upon examination immediately after preparation of the slide. The World Health Organization Expert Committee on Bilharziasis (1953) recommends that centrifuging be limited to 1,000 r.p.m. to obviate the risk of ova disintegrating. I have never, however, found excessive centrifuging, either for too long a time or at too high speed, to cause disintegration of ova.

Dosage

The dosage of nilodin was worked out to give 20 mg. per kg. of body weight per day divided into three equal doses. However, as explained above, the strength of the tablets made it impossible to conform exactly to this amount; consequently, and taking into account reduction of dosage because of toxic symptoms, the average daily dose received by these patients was 22 mg. per kg. No case received less than a 12-day course of treatment, and in one case the treatment extended over 13 days.

Toxicity

Of the 37 cases in which treatment was started 21 (56.7%) had toxic symptoms. These were easily controlled and in no case was it necessary to discontinue treatment, although

the initial dosage of the drug had to be reduced in 11 cases (29.7%). (In two cases the dose had to be reduced on two separate occasions.) A list of toxic manifestations with their frequency is presented in Table I.

TABLE I.—*Toxic Manifestations*

Symptoms	No. of Cases	Percentage of All Cases (21) with Toxic Symptoms	Percentage of All Cases (37) Treated
Nausea and vomiting	12	57·1	32·4
Abdominal pain and discomfort	5	23·8	13·5
Anorexia and nausea	3	14·3	8·1
Suprapubic pain	1	4·8	2·7
Total	21	100·0	56·7

Toxic symptoms first appeared as early as the third day and as late as the tenth day (one case each), the average time being the sixth day. Phenobarbitone, 1 gr. (65 mg.) twice daily, was used to control such symptoms; if this was not effective, the dosage of nilodin was reduced by 200 mg. a day. Although "jaundice" has been reported (Haseeb, 1952) to occur during nilodin therapy, this was not noted in the present series. In all cases there was a very deep reddish-brown pigmentation of the palms and soles, but the conjunctivae were not affected. The urine became bright yellow and so did the tongue—the latter merely from contact with the pills. Examination of the blood on the last (12th) day of treatment in 19 consecutive cases showed that not one had a total serum bilirubin level above 0.5 mg. per 100 ml. and that the highest icteric index was 7. There was no apparent effect upon the kidney glomeruli as evidenced by tests for albuminuria following treatment. Toxic symptoms developed more rapidly and were worse, however, in patients whose renal function was already impaired.

During the 12 days' treatment 22 (59.4%) of the 37 patients had a weight loss ranging from 1 to 17½ lb. (0.45 to 7.7 kg.), with an average of 7 lb. (3.175 kg.). Of these 22 patients 14 complained of toxic symptoms, so that there is a fair correlation between weight loss and toxic effects. Loss of weight was accompanied by a marked diuresis in certain cases.

Results

The clinical response was good. In most cases of frank haematuria the bleeding stopped on about the eighth day; in only two or three cases did it persist, and was then due to granulomata. Patients who continued to pass blood were examined cystoscopically to exclude the possibility of the presence of carcinoma; if there was any doubt a urologist's opinion was sought. In pyrexial cases the temperature responded by the sixth day at the latest, and this response was obtained with nilodin alone. The temperature would probably have fallen much sooner had urinary antiseptics been used to combat the secondary infection which was usually present, but, as the effect of such drugs on *S. haematobium* infection was not known, this might have nullified any claim that the assessment was accurate. Results can be assessed correctly only by an adequate follow-up, which must extend over a period of at least six months. The more examinations which can be made in this period the more accurate will the assessment be.

Of the 24 cases reported five relapsed within the three-month period. In two more cases relapse occurred after this period, in one case eight and a half months and in one six months after treatment. Only ten cases which did not relapse within the first three months could be followed up for six months. There was only one further relapse among these ten cases. Nevertheless, out of 15 cases in which either relapse occurred or the full six-month period of follow-up was completed, six relapsed. (See Table II.) It is therefore obvious that relapse does occur up to, and even after, six months following treatment. I would like to stress that the term "relapse" is here used in its strictest sense. If only one viable ovum or miracidium was observed at any time after the first week following treatment, then that case was considered to have relapsed. In actual fact only one "clinical" relapse occurred.

TABLE II.—*Results of Follow-up Examinations*

Series No.	After Three Months				After Six Months			
	No. of Cases	No. of Re-examinations	No. of Cases Relapsed	% of Cures	No. of Cases	No. of Re-examinations	No. of Cases Relapsed	% of Cures
1	24	13 each	5	79	15	16 each	6	60
2	22	4 „	5	77	18	9 „	12	33

In this series, therefore, we claim to have achieved a 60% "six-month cure," although as this figure does not include the case which relapsed after eight and a half months it is somewhat optimistic. I would, however, stress that, with only one exception, every case was of extremely long standing or chronicity. The cases which relapsed all had very heavy infections, as judged by the number (usually hundreds) of miracidia and ova found at the diagnostic examination.

It is necessary to explain why the cases in which viable ova continued to be passed seven days after treatment cannot be considered as relapses. In the first place it takes an average of six days for nilodin to reach its highest concentration in the serum, as shown by the time taken for the deep pigmentation of the palms, the coloration of the urine, and the toxic symptoms to develop. Therefore the drug is still acting on the worms six days after stopping treatment. Secondly, any ova found at the first re-examination were certainly laid at least 24 hours, and probably three to four days, previously. In chronic cases with much induration, and even calcification, of the bladder wall it may take a considerably longer period for an ovum to penetrate into the lumen of the organ. This being the case, the viability of these ova is no criterion of the state of the parent worms. Once encased within its shell, it is questionable whether the miracidium is as vulnerable to the action of a drug as the adult worm. Furthermore, the eggs lie in the tissue and not in the main blood stream and are thus not exposed to the same concentration of drug. Thirdly, any ova found at the first examination after a 12-day course were not normal; they can only be described as "deformed." Within the ovum large vacuoles and globules had formed, and any movement present was extremely sluggish. When such ova hatch the miracidia are grossly abnormal in shape; the smooth outline is lost, to be replaced by a wavy, irregular periphery; movements are sluggish and the clear protoplasmic outlines are obscured by a degenerate mottling. These changes may have been due to the effect of the drug on the egg-producing organs of the female worm, or possibly on the eggs held up in the tissues.

Of the seven cases in which relapse did occur, three were noted to have viable, though abnormal, ova at the first re-examination. This may be a prognostic point in cases treated with nilodin, as only six cases were observed to have viable ova at the first examination and three of these relapsed later. The mean time of relapse was at the seventh week after treatment.

Series 2

The second series consisted of 22 cases. Every case was seen one week after completing treatment, and thereafter at monthly intervals for six months. Four of the cases did not complete the full six-month period. Four months after completion of treatment every patient was readmitted to hospital for three days, during which time a different method of collecting urine for examination was employed. At all other examinations urine was simply passed into a urine-analysis glass, whereas, in hospital, urine was collected after each patient had taken a 15-minute "ride" on a physiotherapy bicycle every morning for three consecutive mornings. One "24-hour" specimen of urine was also collected. This was voided into a Winchester bottle, and then by a repeated process of decanting and settling a volume of urine and sediment small enough to be centrifuged and examined was obtained.

Dosage

The aim in this series was to give a more concentrated course of treatment over a shorter period. Accordingly the initial dosage was scheduled to be not less than 25 mg. per kg. of body weight per day and the course covered nine days. After the dose had been reduced in two cases because of toxic symptoms the average total dose was 225 mg. per kg. of body weight, so that the average daily dose was in fact 25 mg. per kg.

No specific notes on toxicity were made in this series, as nilodin had been proved by the first series to be relatively non-toxic and without after-effects. In this connexion it will be sufficient to point out that the dosage had only twice to be reduced.

Results

The clinical response was much the same as in the first series. Of 18 cases in which a six-month period of follow-up was completed, 12 (67%) relapsed (Table II). Of these only one was a clinical relapse and 11 were technical relapses. In 7 (58%) of these 12 cases viable ova were found at the first weekly re-examination following treatment. This would seem to confirm that the presence of viable ova at the first weekly re-examination may be a useful prognostic point. In one case relapse occurred seven months after treatment, in this instance a full clinical relapse.

Thus, regarded in the very best light, a 33% "six-month cure" was obtained. Once again this figure is optimistic when it is remembered that one case relapsed after seven months.

Discussion

The results in Series 2 are far worse than those in Series 1, but it is difficult to decide whether this should be attributed to the different scheme of treatment or to the different method of follow-up. A comparison of the three-month post-treatment period in the two series reveals that in Series 1 relapse occurred in 20.8% of cases, or 71.4% of total relapses, whereas in Series 2 the corresponding figures are 22.7% and 38.4%. This difference is due to the fact that the cases in Series 1 had three times as many re-examinations during this period as those in Series 2 (see Table II). A comparison of the six-month results shows that in Series 1 only 15 cases had either relapsed or were still undergoing re-examination. The relapse rate was 40% —6 cases out of 15, including five cases which relapsed in the first three months. In other words, only one new relapse was found in the second three-month period. Of 18 cases in Series 2 which completed the six-month follow-up, 12 (67%) relapsed. This, too, includes five cases which relapsed in the first three months. In this series, however, three cases of relapse were discovered by the special examination at four months described above, without which these cases might have been missed. Excluding these cases the relapse rate was still 50%, as compared with the 40% of Series 1. Four cases were recognized as having relapsed when examined five or six months after treatment, though they had been missed at the four-month special examination. This examination did not prove as effective as it was hoped.

To my mind the follow-up in Series 1 was more adequate than that in Series 2. In the former each case had at least 16 re-examinations in the six months following treatment, whereas in the latter each case had only nine re-examinations in that period. The fact that in Series 2 the results were worse despite a less adequate follow-up would seem to indicate that the important factor in treatment is the length of the course rather than the daily amount of the drug given. Shorter courses of treatment as previously tried have proved, in my experience, even less effective.

In any event the important fact that emerges from this investigation is that even with a nine-day course of treatment only a 33% "cure" can be expected. Even this figure may be too high. In the light of claims that have been made of an 80% cure rate following a five-day course, this should serve as a warning against over-optimism. Such claims can be attributed only to an inadequate follow-up.

It appears from the above that a good method of follow-up would be a fortnightly re-examination for six months following treatment, with a special examination, as described, at the end of that period, and thereafter a monthly examination for another six months.

Mode of Action of Nilodin.—From one to two months after treatment with this drug I have often observed abnormal, non-viable ova in patients' urine which are from one-half to one-third the normal size. Although small, these ova have a perfectly formed shell, but contain only an amorphous mass. They are totally unlike "degenerate" ova which have been held back in the tissues in chronic cases. It is my belief that these may be "sterile" or unfertilized ova, and that the male worm may be more susceptible to treatment than the female. It is also possible that oviposition in the female is affected by the drug, and even temporarily stopped completely. In cases in which such ova are found relapse may occur later or, on the other hand, the urine may become perfectly clear of ova. Another factor is that nilodin may cause temporary immigration of the worms to the liver plexuses. In view of these points it would seem that the only real test of cure would be a complement-fixation test. This would have to be done a fairly long while after treatment.

RECTAL SCHISTOSOMIASIS

In view of the paucity of information about the effect of the newer drugs on rectal infection with *S. mansoni* a short account of our treatment of this condition with nilodin may be of interest. Although a goodly number of cases have been treated, the results in only four cases which have been followed up are presented.

Method of Examination

In all cases in which dysentery was the presenting symptom the diagnosis could be easily arrived at by examination of the faeces, especially of the mucus contained in the stool. Usually the first few fields were enough to demonstrate the presence of ova. The technique used was to tease apart strings of mucus in a drop of tap-water on a slide. The first examination was made with the lowest-power objective lens available. If no ova or miracidia were seen, then a cover slip was placed over the specimen and the high-power lens used in a search for parasites of pathological import. As the clinical manifestations of amoebic dysentery and rectal schistosomiasis so closely resemble each other the differential diagnosis can be made only by an adequate examination of the stools.

In cases without dysentery and in which formed stools were passed examination for *S. mansoni* ova called for a different procedure. In such cases a proctoscope was passed with the patient in the lithotomy position on an operating table. The rectal mucosa was cleaned and then scarified until bleeding occurred by means of a clean swab held in the artery forceps, the mixture of blood and debris removed being transferred to a clean, dry slide. Two slides were prepared in this way so that a fairly large amount of material could be examined. Water was dropped on to the specimen and two cover slips placed on each slide. Slides were examined under the low-power objective of the microscope. In addition all positive cases were examined for the presence of urinary infection.

Every case was re-examined by the direct proctoscopic method—weekly, when possible, for the first three months. Thereafter a monthly proctoscopic examination was conducted until the patient left the employ of the mines. In addition, in every case the urine was examined for *S. haematobium* ova weekly for the first three months and then at monthly intervals while the patient was available. In only one case in this series was there a double infection, *S. haematobium* and *S. mansoni* infesting the urinary tract and *S. mansoni* the rectal plexuses.

Dosage

The daily dosage of nilodin aimed at was 20 mg. per kg. of body weight, though as the tablets of the drug were not divided, as explained above, patients received slightly more

than this amount. Three cases were given a 12-day course of this treatment, but the remaining case had only six days' treatment. No adjuvants were employed apart from intravenous infusion of saline and glucose in two cases in which the patient was suffering from a salt-depletion syndrome on admission to hospital.

Clinical Response

Provided that the patient's general condition was treated adequately, then the response was good. On treatment with nilodin alone, without any antibiotic therapy for the secondary infection, the cases with dysentery made a complete response by the sixth day. It is noteworthy that in many cases (not included in the present series) with symptoms due to stricture of the bowel, treatment of the schistosomal infection had no effect on such symptoms, and where necessary one had to resort to surgery.

Results

Of the four cases here reported not one relapsed clinically during the follow-up period. I stress "clinically" because in one case viable ova were recovered from the rectal mucosa on two occasions after the end of treatment. In another case an inert ovum was recovered on one occasion. This ovum was morphologically normal but the flame cells were not beating. This case should be regarded as having relapsed because, in my experience, successful treatment results in the recovery of macerated ova from the mucosa. The recovery of an inert ovum at the 20th week after treatment, as in this case, should be regarded as highly suspicious.

Results in the four cases are shown in Table III. Two of these cases had previously had courses of "fantorin" (antimony pyrocatechol sodium sulphonate)—in one case two months, and in the other three months, earlier. Both cases had a clinical relapse with the demonstration of viable ova in the stools. They were then given nilodin treatment as described.

TABLE III.—*Results of Follow-up Examinations*

Case No.	Length of Course (Days)	Length of Follow-up (Weeks)	No. of Re-examinations	Clinical Relapse	Technical Relapse	Time of Relapse
1	6	24	14	No	No	—
2	12	23	16	"	Yes	10th and 13th weeks
3	12	22	13	"	?	20th week
4	12	18	11	"	No	—

Discussion

Too few cases are presented for any scientific assessment of the results. However, many more cases have been treated with nilodin although not followed up, and in all the clinical response was good.

The case of mixed *S. mansoni* and *S. haematobium* infection of the bladder is particularly interesting, because during the follow-up period macerated ova of *S. mansoni* were recovered from the urine at 7 out of 15 examinations; on one occasion, too, a macerated ovum of *S. mansoni* was recovered from the rectal mucosa.

The stumbling-block to the correct appraisal of a particular method of treatment in cases of *S. mansoni* infection is the follow-up. There seems to be no really accurate technique available, and certainly none that is simple to carry out.

With the method of follow-up here described I have been pleasantly surprised at the high proportion of positive diagnostic results obtained. At re-examination, however, recovery of ova was variable. In the first of the four cases only one macerated ovum and one macerated miracidium were recovered in the course of 14 re-examinations; in the second case macerated ova were recovered twice, and viable ova twice, in 16 re-examinations; in the third case macerated ova were recovered at seven, and an "inert" ovum at one, of 13 re-examinations; and in the last case macerated *S. mansoni* ova were recovered at only one out of 11 re-examinations of the rectum, while they were present at 7 out of 15 re-examinations of the urine.

When regarded in the light of claims made for other methods of examination our technique would appear to be very poor; but this is no doubt due to the fact that it was applied after treatment—an important point. When used to establish a diagnosis it was highly effective, although no records were kept to substantiate this claim. Furthermore, our results show that if ova are present in the mucosa this technique reveals them. This is exemplified by the third case, in which ova were recovered at 8 out of 13 examinations.

I have come to the conclusion that there is little variation in the susceptibility of *S. haematobium* and *S. mansoni* to nilodin when given in adequate dosage over a long enough period. This contention is well borne out by the case of mixed infection of the urinary tract. For this reason I am of the opinion that research workers should concentrate on urinary schistosomiasis, in which assessment of the results of treatment is much easier and far more accurate.

Summary and Conclusions

Two series of cases of urinary schistosomiasis (*S. haematobium*) occurring in mine-workers in the Transvaal have been treated with nilodin (lucanthone hydrochloride). In the first series (24 cases) an average daily dose of 22 mg. per kg. of body weight was given for twelve days, and in the second (22 cases) a daily dose of 25 mg. per kg. for nine days.

Results did not come up to expectation in either series. A "six-month cure" of 60% was obtained in Series 1 and of 33% in Series 2, the poorer results in the latter being due to what is considered an inadequate course of treatment. One case in each series relapsed after the six-month period of follow-up, so that final results were less good.

Toxic symptoms, though frequent (56.7% of cases), were never severe and were easily controlled. Loss of weight and diuresis were a striking feature in some cases. Toxicity was greater in cases in which there was renal insufficiency.

Results are also given of the treatment with nilodin of four cases of rectal schistosomiasis (*S. mansoni*). Clinical response was excellent. No case of clinical relapse occurred, though in two cases there was a "technical" relapse, as shown by the recovery of viable ova from the rectum.

An interesting case of *S. mansoni* infection of the vesical plexus which was apparently cured by the treatment is described.

Nilodin was found to be easy to administer, and, considering the high percentage of cures if it is adequately used, relatively cheap. It should be stressed that the clinical response to treatment is exceptionally good and that every case benefits in some degree. Treatment should extend over a period of at least twelve days, and preferably sixteen days, and patients should be followed up for at least six months.

It is concluded that, provided an adequate course is given, nilodin is highly effective in the treatment of *Schistosoma* infections in the non-European mine labourer in South Africa; also that the mines of the Witwatersrand and Orange Free State are ideal testing grounds for anti-schistosomal drugs.

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THE TREATMENT OF ASTHMA WITH CORTICOTROPHIN

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Stimulation of the adrenal cortex by adrenocorticotrophic hormone (corticotrophin, A.C.T.H.) has been used with success in various hypersensitivity conditions, and was the subject of a review by Rackemann (1951). Naturally, asthma has featured among the disorders so treated, and further assessment of its use and possible abuse seems desirable in this condition, which has been increasingly recognized as liable to cause a fatal outcome in severe cases. While cortisone has also been used in trials by mouth, by injection, or by inhalation, its use is not here considered.

Present Cases

When the present series of 10 asthmatic cases was treated, A.C.T.H. was still scarce, and certain strict criteria were imposed before giving such treatment: (1) all were admitted to hospital suffering either from severe status asthmaticus or from prolonged and incapacitating asthma; (2) they showed little or no response to other routine forms of therapy, including intravenous aminophylline; and (3) so far as possible, they were unaware that A.C.T.H. was being given lest the idea of some new magic treatment should play a largely psychological part in any improvement. Most of the cases were so severe that it was felt scarcely justifiable or necessary to risk fatalities by a control series such as that usefully described by Ball (1954).

Case 1

A farmer aged 40 had for seven years had repeated infections of the accessory nasal sinuses, requiring operation more than once. Eighteen months before admission he had asthmatic symptoms which were thought to be mainly of infective origin. He entered hospital in a mild status asthmaticus, and treatment, including antispasmodics, penicillin, physiotherapy, and intravenous aminophylline, produced only slight improvement. *X*-ray examination of his sinuses showed widespread infection; he was producing on an average 1 fl. oz. (28 ml.) of purulent sputum daily.

A.C.T.H. was started in a dosage of 30 mg. eight-hourly intramuscularly, and within 36 hours he was much less distressed than he had been for many weeks. The dosage was gradually diminished until a total of 510 mg. had been given in seven days. Two days later he was able to return home in quite a comfortable state.

He started to relapse after a few weeks, and four months after discharge he had to be readmitted urgently. During bronchoscopy under thiopentone anaesthesia he suddenly collapsed and died, and at necropsy his whole bronchial tree was full of sticky mucopurulent secretion.

Case 2

An intelligent and sensible housewife aged 53 was seen at home as an emergency in status asthmaticus so severe that two hours previously her own practitioner had thought her to be on the point of death. In spite of intravenous aminophylline she was still extremely shocked and distressed in her breathing.

She was at once admitted to hospital and given A.C.T.H., 30 mg. intramuscularly six-hourly. Within 12 hours she was comfortable, and within 48 hours she was completely free from wheezing. The total dosage was 730 mg. in nine days.

It was possible to discharge her from hospital on the ninth day, and, although two further admissions were necessary in the next 12 months, she did not require further A.C.T.H. until two years later, when she was readmitted to hospital in a similar, almost moribund, condition. With 100 mg. of A.C.T.H. in the first 24 hours, followed by 200 mg. of A.C.T.H. gel in the next four days, she again made a remarkable recovery.

Case 3

A bill-poster aged 19 gave a six-year history of asthmatic attacks at intervals of some months for no known cause. He was admitted to hospital in severe status asthmaticus, which showed poor and transient response to injections of adrenaline and intravenous aminophylline. Although of fine physique, he was becoming very exhausted, and on the fifth day A.C.T.H. was started. Some improvement was achieved with a total dosage of 425 mg. in five and a half days, but 48 hours after stopping treatment his asthmatic state gradually became worse than ever. No infective element was apparent. After an interval of 12 days, a further course of A.C.T.H. was begun with a higher initial dosage, 150 mg. in the first 24 hours, and on this occasion he showed great improvement within 48 hours. The total dosage for the second course was 500 mg. in seven days, and the patient has remained remarkably well since that time, for a period of over one year.

Case 4

An unemployed man aged 47 dated his asthmatic symptoms from 1940, when he was subjected to blast and exposure followed by evacuation from Dunkirk. From 1950 to 1952 he was under constant out-patient supervision and was twice admitted to hospital for treatment, which had included left hilar denervation; to none of these attempts did he make any satisfactory response and he was never found to be free from some degree of wheezing, although his vital capacity was always well above 4,000 ml. For a few years he had also complained of Raynaud's phenomenon in both hands, and during the two-year period of observation he was unable to resume his work in a tobacco factory.

On his third admission a course of A.C.T.H., 1 g. in 12 days, was given; this produced considerable temporary improvement in his Raynaud's phenomenon, but the relief to his chest was negligible.

Case 5

A housewife aged 36, who had always had a mild asthmatic tendency, had been very much worse since the birth of her child six months previously. She was admitted in status asthmaticus and A.C.T.H. was started; after receiving 120 mg. in 48 hours her chest symptoms were greatly relieved, but mental confusion with euphoria caused the A.C.T.H. to be discontinued.

Within three months she again had to be admitted to hospital in a relapse, which responded to routine measures sufficiently well for her to take her own discharge on the third day.

Case 6

A professional man aged 41, of the keenest intelligence, was one of the series who knew he was receiving A.C.T.H. and appreciated the significance of it. In infancy he had had eczema and in childhood some asthma, which moderated during adolescence. During the preceding five years he had had several attacks of infective bronchitis during the winter, and for three months he suffered numerous bad asthmatic attacks. In view of the possible infective factor of recent years, he was admitted for investigation, including bronchography, which did show dilatation of a few scattered bronchi in either lung.

Possibly, he thought, because of the bronchogram or possibly for psychogenic reasons, he shortly had another severe asthmatic attack, which was unabated after three weeks, by which time his response to intravenous aminophylline was very poor.

He was readmitted, therefore, and A.C.T.H. therapy was started with 30 mg. six-hourly. After the second injection he described a cessation of spasm with a great feeling of relief, and a total dosage of 540 mg. was given in four and a half days. Relapse occurred on two occasions at approximately three-monthly intervals after this, demanding further A.C.T.H. therapy for nine days on each occasion. The results were good, though not quite so remarkable as during the first course.

Case 7

A housewife and schoolteacher, aged 49, with a previous history of "hay-fever" from the age of 18 up to 40, had 10 months previously started getting violent spasms of cough with tenacious sputum, soon accompanied by asthmatic symptoms. She stated that she had not had a single undisturbed night for nine months on this account, and severe exacerbations had occurred on three occasions. She was a nervous woman, severely distressed physically and mentally by constant dyspnoea, and repeatedly in mild status asthmaticus, which was only slightly, if at all, relieved by intensive routine measures, including bronchoscopic aspiration under general anaesthesia. A.C.T.H. gel was given intramuscularly in daily doses of 100, 60, and 60 mg.; and then 40 mg. for seven days.

Great improvement was felt within 24 hours, and within three days she was much clearer than she had been for many months. Although a relapse occurred three months later, it was ultimately controlled by routine measures without A.C.T.H.

Case 8

A housewife aged 54 was the most chronic asthmatic of the whole series. During the 34 years of her trouble she had seen a vast number of doctors, undergone numerous investigations, and received the widest variety of treatments. For eighteen months she had been getting worse than ever, and she stated that for six months she had never been free from wheezing unless she used an atomizer, from which she was inseparable. Every night for five years she had woken in an attack, and it was clear, as she herself admitted, that the psychogenic factor was by far the most important in the aetiology of her asthma.

Worn out mentally and physically as she was by her almost constant mild status asthmaticus, she was given 100 mg. of A.C.T.H. gel intramuscularly one evening at 6 o'clock. At 9 p.m. a kind but unwitting night nurse gave her two codeine compound tablets unaware that she was sensitive to aspirin. Within three hours the patient was in the most severe status asthmaticus, shocked, and almost pulseless, recovery taking place shortly after an intravenous injection of aminophylline, 0.48 g.

Further treatment with A.C.T.H. gel was interrupted for 10 days; she then received a total of 400 mg. in 10 days. By the third day of this course improvement was evident, and by the sixth day she stated that she felt clearer on the chest and better than she had done for many years. At this time her lungs were completely free from adventitious sounds.

She continued fairly well at home for many months after this treatment, requiring many fewer "remedies" than before, although adrenaline injections and her atomizer were still in use. For eighteen months she did not approach a state severe enough to warrant further A.C.T.H. therapy; her husband then started to obtain supplies of A.C.T.H. gel from America, and for many months she had been receiving a maintenance dose of about 20–40 mg. twice weekly. She has not attended for follow-up during this time, but reports from her own practitioner and from her husband seem to indicate clearly that the previous efficacy of the substance is much reduced and may soon be negligible.

Case 9

A woman aged 57 had suffered from asthmatic attacks for many years and had needed admission to hospital on several occasions. Complicating factors were gross sinus infection and scattered fibrosis with bronchiectasis in both lungs. A well-marked psychological element also played a part in perpetuating her symptoms, and when the time came for her to undergo the most necessary sinus operations she admitted that the fear of operation and anaesthesia added very much to her chest troubles. She entered hospital in severe asthma, which was showing scarcely any improvement on routine measures, including intravenous aminophylline. She was despondent and exhausted from lack of sleep. As penicillin was having no effect on her infection chloramphenicol was substituted. After two days, although her sputum was somewhat cleaner, she was still very breathless. A.C.T.H. was started next day, and after 48 hours she showed great improvement physically and mentally. A total dosage of 300 I.U. in six days rendered her well enough to undergo operation in the following week.

Case 10

A retired man aged 72 who had suffered from a cardiac infarct two years previously, had complained of asthmatic symptoms for only about five months before admission, though he had probably experienced mild bronchitic trouble for some years. Since the onset of his bronchospasm, he had had treatment in various parts of the country with numerous medicaments and had on several occasions received a course of A.C.T.H., with the result that he had become very reliant on it and very introspective about his condition.

He was admitted, together with a vast number of drugs and remedies, in severe status asthmaticus, occasioned very largely by the misguided administration of two injections of morphine ¼ gr. (16 mg.), with atropine, 1/100 gr. (0.65 mg.), based on the idea that his asthma might have been of cardiac origin. He had already placed himself again on A.C.T.H., but clearly, after 24 hours, it was making little or no impression on his asthmatic state. Intravenous aminophylline, an iodide mixture, and physiotherapy were much more successful in producing steady improvement, with expectoration of increased amounts of slightly infected sputum.

After two weeks' relative freedom from symptoms his wheezing again flared up acutely, resulting in great

Summary of Cases

Case No.	Sex	Age	A.C.T.H. in mg.	Duration (Days)	Remarks	Response
1	M	40	510	7	Chronic asthma —infected	Good
2	F	53	730	9	Severe status asthmaticus. Comfortable in 12 hours	Excellent
			100 + 200 gel	5	" "	"
3	M	19	425	5½	Status asthmaticus	Moderate
			500 (12 days later)	7		Very good
4	M	47	1,000	12	Chronic asthma	Very poor, but Raynaud's phenomenon relieved
5	F	36	120	2	Status asthmaticus	Good, but treatment stopped on account of mental confusion
6	M	41	540	4½	Status asthmaticus	Excellent—relief within 36 hours
			820	9		Slower improvement
			670	9		" "
7	F	49	500 gel	10	Chronic asthma in mild status	Excellent
8	F	54	400 gel	10	Chronic asthma in status	"
9	F	57	300	6	Chronic asthma with infected bronchiectasis and perisinusitis	Good
10	M	72	415 Several previous courses	8	Recurrent status asthmaticus	Fair

despondency; for two days he struggled on with the previous regime, finding his physiotherapy more and more exhausting, and then he felt he must demand further A.C.T.H. Starting with 30 mg. four-hourly, he experienced relief within eight hours, and was able to be transferred home within 10 days. It was clear that, in this case, the possible psychological effect of having A.C.T.H. could not be excluded; he admitted that it did not have such a dramatic effect in relieving his symptoms as on some previous occasions.

A summary of the salient features of the cases is set out in the Table at the foot of the previous page.

Discussion

In 10 cases of severe and intractable asthma treated with A.C.T.H. the initial response was considered to be very poor in one, fair in one, good in four, and excellent in four; in one of the latter it was probably life-saving on two occasions.

All patients showed relapse of symptoms sooner or later after cessation of treatment, but only three required more than one course of treatment (excepting one who had an immediate relapse). Two of these patients knew they were receiving A.C.T.H., felt the need of it during a severe exacerbation of symptoms, and were agreed that its action was slightly slower and less dramatic on each subsequent occasion.

An initial dosage of 25–30 mg. (I.U.) intramuscularly six-hourly, or even eight-hourly, appeared satisfactory, usually producing great relief within 12–36 hours; it was possible to reduce the dosage after 48–72 hours to 20 mg. eight-hourly for the next two to three days, and then to 10 mg. eight-hourly for a further two days. An average course of seven days' treatment with this diminishing dosage therefore totalled about 450 mg. However, in any statement of dosage used and compared with other authors, it must be remembered that the potency of different extracts may have shown considerable variation. The longer-acting A.C.T.H. gel, used in two cases, seemed just as efficacious as the more standard product, in a daily dosage of about half the amount, and with the added advantage of necessitating only one injection in 24 hours. It is noteworthy, perhaps, that in one of these cases an injection of 100 mg. of A.C.T.H. gel did not prevent a violent asthmatic reaction to aspirin given some three hours later.

In only one patient (Case 3) did the amount of the initial dosage seem important; a higher dose of 150 mg. in 24 hours for an immediate relapse after his first course produced a remarkably good effect, whereas 100 mg. in 24 hours had been somewhat disappointing.

An ill effect was noticed in only one patient: this woman was of rather an unstable temperament, and marked euphoria necessitated stopping treatment after 48 hours. Other reactions are unlikely to be troublesome with the dosage and duration of treatment described, while a mild degree of euphoria may be considered helpful, although not of primary therapeutic importance.

The good effects obtained are not evidently counteracted by some degree of bronchial infection, but in this series measures were being taken simultaneously to treat any such infection with antibiotics and physiotherapy when necessary. In the most heavily infected case (No. 9) it is doubtful if the patient would ever have been rendered fit for her much-needed radical sinus operation without the use of A.C.T.H.

The findings are in agreement with most other authors, that in A.C.T.H. we have a potent substance in the treatment of asthma. Friedlaender and Friedlaender (1951b) gave it to 10 severe chronic asthmatics in a dosage of 52 mg. six-hourly, intramuscularly, with total dosage of 600–870 mg. in 6–13 days. They found dramatic improvement in six patients within 24–36 hours, fair response in two, and no real improvement in two. They pointed out that the relief was of brief duration before recurrence, and that seasonal hypersensitive cases should therefore give the most satisfactory results. Possibly, symptoms recurring after such treatment might more easily be controlled by "conventional" therapy, but the reverse could also occur.

Segal *et al.* (1951) treated 20 severe asthmatics with courses of A.C.T.H. in total dosage of 240–900 mg. over periods of 2½–19 days. As five patients needed more than one course, 27 courses in all were given, and, of these, 24 produced partial or complete remission of symptoms, as follows: eight for one to two weeks, 10 for two to four weeks, and six for four weeks to seven months. They concluded it was better to give short intensive courses of A.C.T.H. therapy rather than try a prolonged maintenance dose.

Rather less impressive results occurred in 18 patients similarly treated by Arbesman (1951), as six of these showed no improvement whatsoever; the average length of remission of symptoms achieved in the rest was three to six weeks. Brown *et al.* (1951) treated 30 chronic asthmatics ambulant over 10 months, the patients giving their own injections and deciding their own requirements, which ranged from 10 mg. twice daily to 12 mg. on alternate days. Relapse of symptoms occurred in all patients soon after cessation of treatment.

Levin (1953) pointed out the benefits of using A.C.T.H. gel; he achieved good or excellent results in 10 adults and six children, some of whom were treated ambulant. One injection of 40–60 mg. was given daily for two to five days; the injections were remarkably painless and there were no undesirable reactions. He considered that with such treatment available the asthmatic should never need A.C.T.H. by intravenous drip.

The exact mode of action of A.C.T.H. in asthma remains somewhat obscure. Elkinton *et al.* (1949) made careful studies in a 12-year-old boy to assess whether adrenal cortical stimulation was proportional to the clinical improvement. With eosinophil blood counts, balances of chloride, sodium, sugar, potassium, and nitrogen, and study of 17-ketosteroids they could find no such correlation, and it has been suggested from the findings that in asthma the beneficial effect may depend upon some special function of the hormone. The lack of any definite correlation between clinical response and the eosinophil count has been confirmed by Friedlaender and Friedlaender (1951a) and by Feinberg *et al.* (1951).

It cannot be over-emphasized that the treatment described should in no way replace attempts at full assessment of the asthmatic case, so that more rational and radical therapy can be given whenever possible. If used, it is thought preferable that the patient should not know what he is receiving, as, if its dramatic effect is evident to him, he may demand it for ever afterwards when distressed, and morally it may prove very difficult for the practitioner to withhold it. In fact, one can visualize the asthmatic almost as addicted to A.C.T.H. as, say, to his inhaler, and, worse still, if used too often this substance might gradually lose its beneficial effect, a point strongly suggested by two cases in the present series. I am also of the opinion that, at present, it is wiser to restrict the use of A.C.T.H. to the relief of a severe exacerbation of symptoms by a short course, to be repeated if necessary.

Conclusions

A.C.T.H. is most efficacious in the treatment of severe status asthmaticus, and can be life-saving when all else fails.

As it should not be necessary in such a case for treatment to last for more than five to nine days, very few ill effects are to be expected.

An average initial dosage of 25–30 mg. six-hourly is satisfactory, and must be reduced gradually after improvement has occurred, usually within 48 hours.

It is suggested that the use of A.C.T.H. should at present be restricted to very severe cases that are resistant to other forms of treatment, and, if possible, the patient should not know what he is receiving.

Heavily infected cases respond as well as others do, but should be treated with extra caution.

There is no convincing evidence in the present series or in published cases to suggest that a longer remission of symptoms occurs after A.C.T.H. therapy than after any other treatment which succeeds.

A.C.T.H. in no way avoids the expediency of all the other established methods in the assessment, treatment, and management of the asthmatic case.

Summary

The use of adrenocorticotrophic hormone is described in 10 asthmatics. In eight of these there was a remarkable relief of severe acute respiratory distress, resistant to other forms of therapy.

It is suggested that this substance should at present be used in asthma only as an emergency measure.

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EXCHANGE TRANSFUSION AS A MEANS OF REMOVING BILIRUBIN IN HAEMOLYTIC DISEASE OF THE NEWBORN

BY

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Damage to the brain occurs with varying frequency in haemolytic disease of the newborn. Exchange transfusion, as ordinarily carried out, is not entirely effective in preventing it.

It is now known that brain damage is found in association with a great excess of plasma bilirubin in the following conditions: (1) haemolytic disease of the newborn from iso-immunization relative to blood-group antigens D, E, A, and S; (2) prematurity without haemolytic disease; and (3) some types of "familial" hyperbilirubinaemia. Claireaux *et al.* (1953) have shown that in the first two conditions the yellow pigment in affected brains is the indirect-reacting plasma bile pigment, bilirubin. They have reviewed the evidence that this pigment is damaging to brain tissue, and that the direct-reacting bile pigments are innocuous. Some further indications of the toxic character of bilirubin have been published by Lathe (1954).

A more detailed study of the pigment changes in haemolytic disease of the newborn was undertaken with a view to developing methods of avoiding its accumulation. It seemed possible that the role of bilirubin would be made clear from the clinical results of preventing high plasma bilirubin concentrations in infants with haemolytic disease. An encouraging report by Hsia, Allen, Gellis, and Diamond (1952) and Hsia (1953) has now come to our attention. The work described here confirms their observations regarding the pattern of bile pigment changes in the plasma in haemolytic disease, and shows that it is possible to control the plasma bilirubin concentration by exchange transfusion.

Methods and Materials

Clinical Material.—Observations have been made on a series of infants affected with haemolytic disease at this hospital. The brief clinical descriptions of six of these have been drawn from the case records. Serological data have not been included individually, since there was a common basis for serological diagnosis of haemolytic disease in all six cases: (1) mother's group was Rh-negative, (2) maternal antibodies were present, (3) infant's group was Rh-positive, (4) infant cells gave a positive test with rabbit anti-human globulin serum (Coombs +). The blood specimens removed at exchange transfusion of three infants at the Hammersmith Hospital have also been available for study. *Blood specimens* were taken from heel pricks when not otherwise stated. *Haemoglobin* estimations were made with a visual *colorimeter* (M.R.C. grey wedge) which was suitably calibrated—100% haemoglobin being taken as 14.8 g. per 100 ml. *Bile pigment* estimations were made on serum and plasma by the method of King (1951). In Cases 1 and 2 the relative proportions of direct- and indirect-reacting pigments were estimated semi-quantitatively by the appearance of pigment bands on chromatography columns (Cole and Lathe, 1953). In Cases 4, 5, and 6 the proportions of the two types of pigment were determined quantitatively by the method of Malloy and Evelyn (1937).

Plasma Bilirubin in Haemolytic Disease

No detailed study of bile pigment metabolism in a series of untreated cases of haemolytic disease of the newborn has yet been published. That such a study would have shown a wide variation from case to case is suggested by the data of Hsia, Allen, Diamond, and Gellis (1953), and of Mollison and Cutbush (1954). In this hospital there has been an opportunity of studying a number of affected infants who were not given an exchange transfusion because the cord blood contained more than 105% haemoglobin. Some of these infants later gave evidence of a considerable haemolytic process as shown by the changes in haemoglobin and plasma bile pigments. Two contrasting cases are described. Case 1 is an instance of haemolytic disease in which no exchange transfusion was given. In Case 2 only a simple transfusion was possible.

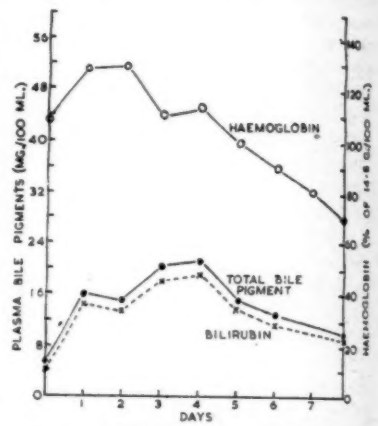

FIG. 1.—Changes in concentration of blood haemoglobin and of plasma bile pigments in Case 1.

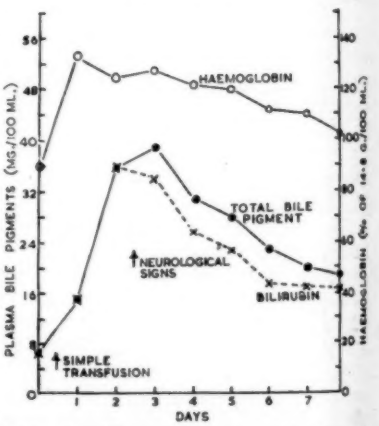

FIG. 2.—Changes in concentration of blood haemoglobin and of plasma bile pigments in Case 2.

Case 1 (Fig. 1).—Two previous siblings were unaffected. The gestation period was estimated at 39 weeks. The birth weight was 8 lb. 5 oz. (3.7 kg.) and the cord haemoglobin was 109%. Cord serum bile pigment was 5 mg. per 100 ml. The infant looked slightly yellow at birth, but its condition was otherwise satisfactory. Jaundice deepened within 24 hours and lasted about a week. The blood haemoglobin concentration dropped at the rate of 8% per day for 11 days. The plasma bile pigment concentration reached a peak of 21 mg. per 100 ml. on the fourth day. No neurological signs appeared. A simple transfusion was later given to correct the anaemia.

Case 2 (Fig. 2).—There were two previous unaffected siblings. The period of gestation was estimated at 37 weeks. At birth the infant weighed 7 lb. 2 oz. (3.2 kg.) and was pale and limp. The cord blood contained 90% haemoglobin. The serum contained 6.3 mg. of bile pigment per 100 ml. Attempts at exchange transfusion failed and 128 ml. of blood was given as a simple transfusion. Following this, the blood haemoglobin fell consistently at the rate of 4.2% per day for 15 days. The plasma bile pigment rose rapidly, and when it was between 36 and 38 mg. per 100 ml. the neurological behaviour became abnormal, with irritability, head retraction, arms held stiffly extended, increased muscle tone, and disinterest in feeding. The plasma bile pigment began to drop about the third day, and fell below 20 mg. about day 6. Although much improved, the baby had not recovered normal neurological behaviour in eight months.

Course of Plasma Bile Pigment in Exchange Transfusion

It is apparent from examining a number of graphs of the rise and fall of plasma pigment in neonatal haemolytic disease that high concentrations of bile pigment are not sustained for long. Not infrequently the period of exposure to high concentrations does not exceed 36 or 48 hours. This encouraged us to seek a means of maintaining a low pigment concentration during this critical period. In the course of studying the amount of bile pigment removed at exchange transfusion it was observed that in large transfusions the blood withdrawn during the procedure contained more bile pigment than the baby's blood volume was calculated to contain at the beginning. This could be explained only by a passage of pigment from the tissues into the circulation during the transfusion. To examine this point, the bile pigment was quantitatively estimated in each specimen of blood removed in a number of exchange transfusions.

The course of plasma bile pigment concentration, together with the calculated extent of blood replacement, at each stage throughout one exchange transfusion, is plotted in Fig. 3. The replacement of the infant's blood did not lower the plasma pigment as much as was calculated on the basis of blood exchanged. It was concluded then that the plasma pigment concentration was partly sustained by removal of pigment from the tissues. The overall effect on bile pigment concentration of 10 exchange transfusions, given immediately after birth for the purpose of removing infant red cells and maternal antibodies, and studied in this way, is given in the Table (A).

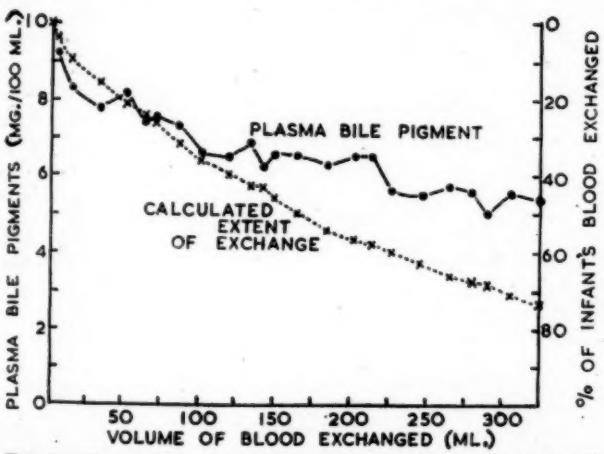
PLASMA BILE PIGMENT
CALCULATED EXTENT OF EXCHANGE
PLASMA BILE PIGMENTS (MG./100 ML.)
% OF INFANT'S BLOOD EXCHANGED
VOLUME OF BLOOD EXCHANGED (ML.)

FIG. 3.—Changes in concentration of plasma bile pigment, and the extent of replacement of the infant's blood, throughout an exchange transfusion immediately after birth. (Birth weight, 6 lb. 10 oz.—3 kg.)

Change in Plasma Bile Pigment During Perfusion with Blood

Birth Weight		Exchange		Plasma Bile Pigments		
				Initial (mg./100 ml.)	Final (mg./100 ml.)	Decrease %
A. Exchange Transfusion at Birth						
lb.	kg.	ml./lb.	ml./kg			
5·9	2·67	68	150	7·0	4·8	31
6·6	2·99	51	112	9·2	5·3	42
5·4	2·45	41	90	7·8	4·4	44
6·7	3·09	63	139	3·2	2·2	31
6·5	2·95	75	165	10·9	2·6	76
5·8	2·63	51	112	5·1	3·6	29
5·7	2·58	62	136	10·2	5·6	45
7·0	3·18	62	136	5·0	4·0	20
7·1	3·22	81	178	8·2	6·0	27
7·7	3·49	96	211	10·8	4·8	56
B. Transfusions Because of Hyperbilirubinaemia						
9·1	4·13	39	86	16·0	14·5	9
7·0	3·18	71	156	38·0	26·0	32
6·5	2·95	35	77	17·3	9·1	47
5·7	2·58	61	134	24·0	11·6	51
5·7	2·58	42	92	20·4	10·5	48
7·5	3·40	54	119	23·3	14·0	40
7·1	3·22	105	231	21·9	8·0	60
6·4	2·90	71	156	20·2	12·1	40
6·5	2·95	61	134	21·0	15·7	25
7·4	3·36	60	132	21·3	10·8	49

Treatment of Hyperbilirubinaemia

Since it seemed that exchange transfusion could be used as a means of washing bilirubin out of the tissues of affected infants, it was next applied to babies that had not been given exchange transfusions at birth (cord blood haemoglobin greater than 105%), but in whom a marked rise of plasma bilirubin was noted during the neonatal period. In the first instance of this (Case 3) the exchange transfusion was not made until neurological signs of damage had appeared.

Case 3.—Two previous siblings were unaffected. The mother had had one miscarriage. The gestation period was estimated at 41 weeks. At birth the infant weighed 7 lb. ½ oz. (3.2 kg.). The concentration of haemoglobin in the cord blood was 111%. The cord serum bile pigment was 1.9 mg. per 100 ml. The liver and spleen were not palpable. The plasma bile pigment at 12 hours was 7.7 mg. per 100 ml. Icterus appeared at 18 hours and became severe at 24 hours. The plasma bile pigment was 19.3 mg. per 100 ml. at 36 hours. It continued to rise, and on the third day head retraction appeared, and there were periods of limb extension, grimaces, etc. Plasma bile pigment was then 38 mg. per 100 ml. An exchange transfusion of 71 ml. per lb. (156 ml. per kg.) was made. During it, opisthotonos developed. The transfusion reduced the bile pigment from 38 to 26 mg. per 100 ml. The pigment rose again to a peak of 32.5 mg. on day 5; it then dropped to 12 mg. during the ensuing two days. The neurological signs had meanwhile improved. At four months a diagnosis of cerebral palsy was made.

The following case is a more typical example of an exchange transfusion which was undertaken when the pigment concentration reached 20 mg. per 100 ml.

Case 4 (Fig. 4).—The mother had one previous infant without any sign of haemolytic disease. The membranes were ruptured artificially during the 38th week because

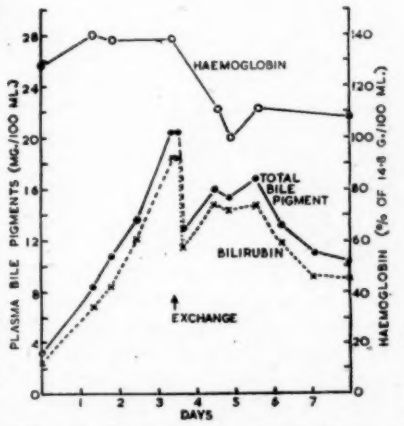

FIG. 4.—Changes in concentration of blood haemoglobin and of plasma bile pigments in Case 4.

of diminished foetal movements. Caesarean section was undertaken three days later because labour had not started. The birth weight was 6 lb. 6 oz. (2.9 kg.), and cord blood haemoglobin was 128%. Cord serum bile pigments were 3.4 mg. per 100 ml., of which 2.6 were bilirubin. Jaundice appeared in 24 hours and deepened as the bile pigment rose to 20.2 mg. on the third day. An exchange transfusion of 71 ml. per lb. (156 ml. per kg.) reduced the pigment to 12.1 mg. per 100 ml. On the following (fourth) day it rose again, but after the fifth day it fell consistently. No neurological signs appeared.

This pattern of change in plasma pigment concentration is probably the one most often observed among infants of substantial weight which are not seriously affected at birth and for whom an exchange transfusion is later performed because of rising bilirubin. The rise of pigment may be much more abrupt, however, reaching 20 mg. per 100 ml. in 24 hours. The Table (B) shows the overall effect on bile pigment concentration of 10 transfusions given because of the elevated plasma pigment. Each of these was studied throughout the whole of the transfusion. Some of these were repeat transfusions.

Obstruction Due to Haemolytic Disease

Note must be taken of the type of bile pigment present in each individual case of haemolytic disease of the newborn. In early studies of haemolytic disease, and of jaundice of the newborn in which there is no excessive haemolysis (Billing *et al.*, 1954), the type of pigment present in the plasma was examined in many cases. The predominating pigment was bilirubin, and direct-reacting pigment I and II (Cole *et al.*, 1954) were present in much smaller amounts. For a period, because of the small amounts of these direct-reacting pigments, the relative proportions of the direct pigments and bilirubin were not estimated. That this practice may lead to serious error is indicated in Case 5 and Case 6.

Case 5.—Two previous siblings showed jaundice at the third and first days of life, respectively, and the second infant died. The pregnancy was complicated by toxaemia, which necessitated a surgical induction of labour at the 37th week. The weight at birth was 5 lb. 11 oz. (2.6 kg.), and cord haemoglobin was 75%. Cord serum bile pigment was 6.3 mg. per 100 ml. The liver and spleen were greatly enlarged. The infant became jaundiced within three hours. It was given an immediate exchange transfusion of 62 ml. per lb. (136 ml. per kg.), which reduced the plasma bile pigment from 10.2 to 5.6 mg. per 100 ml. Within 24 hours the pigment had risen to 19 mg., and the rise continued to 24 mg. at 48 hours, when a second exchange transfusion of 61 ml. per lb. (134 ml. per kg.) was made. At the conclusion the bile pigment had dropped to 11.6 mg., but it rose to 20.4 mg. in another 12 hours. Some indefinite neurological signs (grimacing and twitching) were reported by the nursing staff. A third exchange transfusion of 42 ml. per lb. (92 ml. per kg.) at 75 hours reduced the pigment to 10.5 mg. It rose again 12 hours later to 18.4 mg. and remained between 18 and 20 mg. for another 36 hours, when it rose to 24 mg. At this point the character of the bile pigments was examined for the first time, and it was found that, of a total bile pigment of 24 mg. per 100 ml., only 5.3 mg. was bilirubin. In the light of this evidence that obstruction was the dominant feature further transfusions were not made. The total bile pigment remained between 22 and 24 mg. per 100 ml. (bilirubin 5.6 mg.) until the middle of the sixth day, when it dropped within 24 hours to 13.2 mg. per 100 ml., of which bilirubin was 3 mg. The infant's condition at three months was satisfactory.

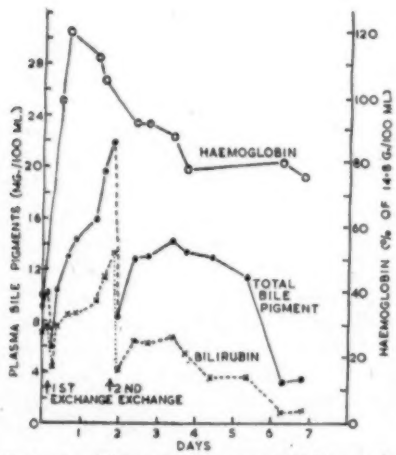

FIG. 5.—Changes in concentration of blood haemoglobin and of plasma bile pigments in Case 6.

The amount and type of pigments present in the early stages of this case are not known. The only specimen which had been preserved was the cord serum (total pigment 6.3 mg.), which contained equal parts of bilirubin, pigment I, and pigment II, as determined by Billing (1955).

Case 6 (Fig. 5).—The mother had three previous infants. The third, which was affected with haemolytic disease, was given an exchange transfusion, following which it developed marked signs of brain damage, which persisted until death at 10 months. The present infant was 7 lb. 2 oz. (3.2 kg.) at birth. The gestation period was uncertain. The cord blood haemoglobin was 39% and plasma bile pigment 9.2 mg. per 100 ml., of which 6.8 mg. was bilirubin. The liver and spleen were greatly enlarged. Although the clinical condition at birth was precarious, it improved greatly during the course of an exchange of 81 ml. of blood per lb. (178 ml. per kg.). Because of the desire at all costs to avoid a repetition of the tragedy of the previous sibling, and because of uncertainty concerning the significance of the direct-reacting pigment, a second exchange—105 ml. per lb. (231 ml. per kg.)—was given on the second day, when the plasma bile pigment concentration was rising rapidly. It never again reached dangerous concentrations. No abnormal neurological signs appeared.

Discussion

Liver Function

The cases which have been presented illustrate some of the fundamental aspects of bile pigment metabolism in the newborn infant affected with haemolytic disease. The plasma bilirubin concentration is determined partly by the rate of pigment formation in the reticuloendothelial system, but also by the rate at which the pigment is removed by the liver. In all newborn infants this latter capacity is probably very much reduced, and in many of the small infants the reduction is extreme—down to 1 or 2% of normal (Billing *et al.*, 1954). These small infants also take much longer to develop an adequate excretory ability.

Among infants of normal weight there is considerable variation in the excretory capacity of the liver at birth and immediately after it. This may be seen by comparing Cases 1 and 2. Although the haemoglobin concentrations fell in the first case at approximately twice the rate of the second, the peaks of bile pigment concentration are of an inverse order. The apparent difference in liver capacity may arise in part from the disparity in birth weights—8.3 and 7.1 lb. (3.8 and 3.2 kg.) respectively—and in the estimated gestation periods (39 and 37 weeks respectively). The changes of plasma bile pigment concentration in these cases also illustrate the way in which the capacity of the liver to excrete bilirubin develops rapidly during the neonatal period, since in both cases the loss of haemoglobin appears to have taken place at a relatively constant rate. It is this change in liver capacity which gives the dramatic character to the rise and fall of bile pigment (Fig. 2), and not any sudden acceleration of the haemolytic process in the neonatal period, as is often inferred. Indeed, in small premature infants unaffected with haemolytic disease the same thing takes place (on a reduced scale).

Removal of Bilirubin by Perfusion

The bilirubin produced from haemoglobin does not remain free in the body fluids, but attaches itself to various constituents, and in particular to plasma albumin, which has a marked affinity for it. At abnormally high plasma pigment concentrations appreciable amounts of bilirubin pass out of the circulation and become attached to other body constituents. This process may be reversed by the continuous replacement of the pigment-laden plasma proteins of the infant with protein which is free of pigment. This is demonstrated by the course of plasma bilirubin concentration throughout an exchange transfusion (Fig. 3). The extent of this shift of pigment from the tissues is indicated by the area between the two curves in Fig. 3. The Table shows that a perfusion of 50–60 ml. per lb. (110–132 ml. per kg.) fairly consistently results in a drop of plasma pigment concentration of 30–50%.

After an exchange transfusion the bile pigment of the plasma nearly always rises again for a variable period. Although this may partly be due to a movement of further pigment out of the tissues, it seems that the previous trend of rising pigment concentration is continued in some degree, but at a lower level, until the liver capacity becomes sufficiently developed to remove bilirubin at the rate at which it is being formed. However, another aspect must also be considered. The baby receives at transfusion a very large amount of preserved blood. In the presence of an already overtaxed ability to excrete bilirubin any breakdown of the transfused blood will add to the accumulated pigment. Recent papers reveal that 10–20-day-old blood is still being used for exchange transfusion. Breakdown of 10% of such blood would lead to the accumulation of another 25 mg. of bilirubin per lb. (55 mg. per kg.) of body weight, from which a marked rise of plasma bilirubin would follow. Because of the limited capacity of the liver to dispose of bilirubin, newborn infants require a more rigorous criterion for adequate preservation of blood than do adults. For this reason some blood depots now adopt the highly desirable procedure of issuing the blood drawn during the previous 24 hours for exchange transfusions.

"Inspissated Bile Syndrome"

The predominant plasma pigment of haemolytic disease of the newborn (Claireaux *et al.*, 1953), as well as that of non-haemolytic neonatal jaundice (Billing *et al.*, 1954), is bilirubin, which is indirect-reacting in the van den Bergh test. The occasional appearance of large amounts of direct-reacting pigments I and II due to obstruction resulting from haemolytic disease is demonstrated in Case 5 and Case 6 (Fig. 5). The simultaneous appearance of direct-reacting pigments in the plasma and of bile thrombi was noted by Aschoff (1924) in experimental haemolytic anaemia in dogs. The same relation probably holds in some severe cases of haemolytic disease of the newborn. Bile thrombi have been described (Claireaux, 1950), and direct-reacting pigment may predominate as seen above. Hsia, Patterson, Allen, Diamond, and Gellis (1952) have called attention to the fact that haemolytic disease of the newborn is a frequent cause of the "inspissated bile syndrome." It may be significant that the three cases of haemolytic disease in which we observed considerable direct-reacting pigment at birth, or shortly after, had hepatomegaly at birth.

The occasional appearance of much direct-reacting pigment emphasizes the great need for further work to establish unequivocally whether or not the direct-reacting pigments are damaging to the brain, since the evidence on this point is not yet conclusive enough to allow one to withhold exchange transfusion with equanimity.

Factors Affecting Transfusion

The facility with which high concentrations of plasma bilirubin can be prevented by exchange transfusion will depend on (1) the rate at which bilirubin is produced in the infant, (2) the effectiveness of the individual exchange operation, (3) the concentration of pigment which is considered to be a serious threat to the baby, and (4) the length of time required for the liver to attain adequate excretory function. In an affected infant the rate at which bilirubin is produced is greatly reduced by removing the infant's own cells, and where there are indications for doing this at birth it is the single most effective measure which can be taken to protect the infant. The limitation of a single exchange transfusion lies in the fact that as it proceeds it becomes increasingly inefficient in the removal of affected red blood cells. However, as shown in Fig. 3, this limitation does not apply to the same extent to the removal of bilirubin, the amount of which will be determined in large measure by the volume of blood with which the infant is perfused. Thus, under some circumstances, where the infant is quite robust and the plasma bilirubin is dangerously high, there may be some justification for increasing the amount perfused to 100 ml. per lb. (220 ml. per kg.), as was done at this hospital on one occasion.

Toxic Level of Bilirubin

Treatment is directed toward preventing a rise of plasma bilirubin above the level at which the incidence of brain damage becomes appreciable. Mollison and Cutbush (1954) state that at plasma concentrations of total bile pigment of 19–24 mg. per 100 ml. 1 baby in 13 suffered brain damage, and that this increased to 4 out of 12 if the amount of pigment rose to 24–29 mg. per 100 ml. Above that amount the majority of infants were affected. Similar results have been observed by Hsia, Allen, Gellis, and Diamond (1952) in a series of 229 infants affected with erythroblastosis: "Kernicterus occurred in 18% of the infants whose serum bilirubin was recorded at a level between 16 and 30 mg. per 100 c.cm., and in 50% of those in whom levels above 30 mg. per 100 c.cm. were seen."

It has been suggested that, in addition to other indications, an exchange or re-exchange transfusion should be done each time the plasma bilirubin concentration rises to 20 mg. per 100 ml. or above (*British Medical Journal*, 1954; Crosse *et al.*, 1954). Hsia (1953) reported that in 250 cases of erythroblastosis in which exchange transfusions were performed each time bilirubin exceeded 20 mg. there were no cases of kernicterus. The experience of undertaking exchange transfusions when the bilirubin reaches 20 mg. per 100 ml. shows that, in general, an exchange transfusion maintains the pigment concentration below the danger level for one or two days. Thereafter perfusion has to be repeated unless the pigment excretory capacity of the liver has developed to an adequate extent.

Small Infants

Small infants are more likely to require repeated transfusions, since, on the average, they need a longer period for the development of the capacity to excrete bilirubin (Billing *et al.*, 1954). It may be noted, too, that the occurrence of brain pigmentation in jaundice of premature infants that are unaffected with haemolytic disease, as well as the greater incidence of brain damage among premature than mature infants with haemolytic disease (Allen *et al.*, 1950; Armitage and Mollison, 1953), suggest that small infants may be more sensitive to bilirubin, and thus may need to be protected against bilirubin concentrations of less than 20 mg. per 100 ml. of plasma. These two aspects of the small newborn infant should be taken into account when premature delivery of infants (Watson *et al.*, 1954) is being considered.

The possibility of successfully treating infants that are severely affected with haemolytic disease (and even of premature infants) is considerably extended by the fact that the concentration of plasma bilirubin can be controlled. Of course, this does not provide a reason for delaying an initial exchange transfusion for the purpose of removing the infant's sensitized cells. On the contrary, it emphasizes the necessity of doing this as soon as there is an indication of a serious haemolytic condition. In the first instance the cord haemoglobin is of major importance, but a later rapid rise of plasma bilirubin may be a significant warning.

Summary

The changes in concentration of plasma bile pigments have been followed in cases of haemolytic disease of the newborn and throughout exchange transfusions. A drop of 30–50% in the concentration of plasma bile pigment is usually brought about by exchange transfusion, during which bile pigment is washed out of the tissues. By one or more transfusions the bilirubin concentration may be kept below the level at which the incidence of brain damage becomes appreciable. The number of times

perfusion has to be repeated will be influenced by the speed with which the liver develops the capacity to excrete bilirubin.

Because of the underlying hepatic deficit in the newborn baby the importance of using recently drawn blood for transfusion is stressed.

The significance of the large amounts of direct-reacting bile pigment that have been shown to occur in the plasma of some cases of haemolytic disease is discussed.

This study has been made possible by the close co-operation of Miss M. Ashforth in following the clinical condition of the infants and in securing specimens for analysis. She has also been responsible for most of the exchange transfusions. I am grateful to Dr. A. White Franklin for opportunities of studying infants under his care. The serological and haematological examinations have been supervised by Dr. John Murray. Specimens from the Hammersmith Hospital have been obtained with the help of Professor J. McClure Browne and Dr. J. Dean. I am also grateful to P. G. Cole, C. R. J. Ruthven, and S. Bebbington for skilled laboratory assistance, and to Dr. John Murray, Dr. A. E. Claireaux, and Dr. Barbara H. Billing for frequent discussions and suggestions.

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Believed to be the only unit of its kind ever to be formed in the British Army, the Parachute Medical Team is described by Dr. J. S. Macdonald in the *Journal of the R.A.M.C.*, January, 1955. It is staffed by personnel of the 16th Independent Parachute Brigade Group and operates in the Middle East. On receiving a signal that an aeroplane has crashed in the desert, the team sets off in a "Valetta" aircraft standing by and fitted out specially for the dropping of men and containers. On finding the crashed aircraft, a suitable dropping zone is sought, a smoke canister thrown out to determine wind speed and direction, and then the medical officer and nursing orderly jump. If they find that further help is needed, they fire a green Very cartridge, and the rest of the team follow—namely, three privates R.A.M.C., and one corporal and two signalmen Royal Signals. (The main duty of one of the signalmen is to carry a radio set down, since this is still the surest way of getting these delicate instruments to the ground intact.) If the first two to jump find they do not need any assistants, they fire a red Very light, and the aircraft drops food and water. The team's task is to give such first-aid treatment as may be required until the R.A.F. ground rescue team can arrive and take them all to safety. The equipment parachuted includes intravenous fluids, splints, morphine, anaesthetics, surgical instruments, antibiotics, and a bivouac tent to provide that most longed-for solace in the desert—shade.

ALDOSTERONE IN URINE OF NORMAL MAN AND OF PATIENTS WITH OEDEMA

ITS INCREASED RECOVERY AFTER HYDROLYSIS WITH ACID AND WITH BETA-GLUCURONIDASE*

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Neutral lipid extracts of acidified urine from patients with the nephrotic syndrome, in heart failure, and in some other oedematous states cause sodium retention and potassium elimination when injected into adrenalectomized rats (Deming and Luetscher, 1950; Luetscher *et al.*, 1952; Luetscher and Johnson, 1954b; Chart and Shipley, 1953; Singer and Wener, 1953; Gordon *et al.*, 1954). The substance responsible for this mineralocorticoid activity has been separated by paper chromatography from urine extracts (Luetscher and Johnson, 1954a). Further work (Luetscher, 1955; Luetscher, Neher, and Wettstein, 1954) has shown that this sodium-retaining corticoid is identical with aldosterone (Simpson and Tait, 1953; Simpson *et al.*, 1954) in the following ways: (1) its high sodium-retaining potency in bioassay; (2) its absorption of ultra-violet and of infra-red radiations; (3) its reducing activity; (4) its melting point, and (5) the chromatographic mobility of the native substance, of its mono- and di-acetates, and of its oxidation products after treatment with periodate.

Cope and Garcia-Llaurado (1954) found a substance of similar chromatographic behaviour in the urine of a woman suffering from a severe potassium-losing condition. Their extracts of neutral urine from normal men yielded only traces of activity. Luetscher and Axelrad (1954) obtained a much larger yield of aldosterone from normal urine which had stood for a day at *p*H 1. Venning *et al.* (1954) found increased amounts of sodium-retaining substances in urine treated with beta-glucuronidase. Thus the amount of active material extracted depends partly upon the method of hydrolysis. This report compares the yields, after various methods of hydrolysis, from urine of normal subjects on their usual diet and after salt restriction. The present study also includes data on the hydrolysis of urine of patients showing an increased urinary output of sodium-retaining material.

Methods

Urine was immediately stored in a refrigerator without preservative. The total 24-hour specimen was mixed, the volume was recorded, and a small aliquot was set aside for chemical analysis. The remaining urine was frozen and stored at −20° C. until extraction. Immediately before extraction, urine was brought to 20° C. and the *p*H was adjusted as indicated.

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Methods of Hydrolysis.—"Neutral" (N): These extracts were made at once after adjusting the urine to *p*H 6.5 ± 0.1. "Immediate Acid" (A): Urine was extracted within 40 minutes after acidification to *p*H 1. "24-hour Acid" (B): Urine which had already been extracted within 40 minutes at *p*H 1 was then allowed to stand at 20° C. at the same *p*H for 24 hours; it was then re-extracted. "Control for Glucuronidase" (Cg): Urine was adjusted to *p*H 4.8, and 0.02 volume of 5 molar acetate buffer of *p*H 4.8 was added. The specimen was then incubated at 37° C. for the specified time over 50 to 100 ml. of chloroform. The *p*H did not change appreciably during incubation. "Glucuronidase" (G): Specimens were prepared as described for Cg and were incubated with the enzyme (Cohen, 1951). Concentrated beta-glucuronidase prepared from calf spleen (Vio-Bin Corporation, Monticello, Illinois) was used in the first experiments. Subsequently, a solution of purified beta-glucuronidase, derived from beef liver, was obtained from the Warner-Chilcott Laboratories, New York. The activities, measured by the method of Talalay *et al.* (1946), were of the order stated by the makers. The various concentrations and times of incubation at *p*H 4.8 and 37° C. are noted in the tables. When urine was extracted by method A before treatment with glucuronidase, the symbol AG is used.

Extraction.—Extracts were made by shaking the hydrolysed urine with four aliquots of chloroform (0.1 volume per volume of urine, but not less than 100 ml. per aliquot). Emulsions were broken by centrifugation.

Alkali Wash.—All chloroform extracts except those designated AU in Table I were cooled to 5° C. and washed twice with cold 0.1 N solution of sodium hydroxide and once with cold distilled water. The combined aqueous washings were acidified and re-extracted with chloroform only in a few instances (Table I). Chloroform was removed under reduced pressure below 40° C. Extracts were stored in 95% ethanol at 0° C.

Chromatography.—The system used was toluene-propylene glycol (Burton *et al.*, 1951). "Fraction E" is that which contains cortisone and aldosterone in this system. In a few instances other systems described by Bush (1952) were also used.

Bioassay.—The method was described by Johnson (1954). Groups of nine adrenalectomized rats were used. Results are expressed as that dose of deoxycortone acetate (D.C.A.) which would produce in the rats an equivalent response in urinary potassium-to-sodium ratio. The 95% confidence limits of this estimate are ±2.15 μg. D.C.A. in a range of dosage from 0 to 10 μg. D.C.A. assayed in a group of nine rats. In all assays the effect on sodium output has also been calculated, and has been found to agree well with the more precise estimates based on potassium-to-sodium ratio. The term "sodium-retaining activity" has been used because this is the predominant effect measured in the bioassay. In those instances in which the test material caused increased excretion of sodium the estimate of dosage as μg. D.C.A. has a minus sign.

The dose of extract given to each rat is a known fraction of the patient's 24-hour urine extract. Each dose is expressed in minutes; for example, 20 minutes is 1/72 of the extract from one day's urine (1,440 minutes).

Effect of pH and Alkali Wash

Extracts made from urine at *p*H 6.5 showed insignificant sodium-retaining activity in a dose of 20 minutes (Table I, N). When the same urine was acidified to *p*H 1 before extraction, significant activity was found in 20-minute doses from two patients (Ro., nephrosis with oedema, extracts AU and A; Ph., cirrhosis with ascites, extract A), but not in the extract from a healthy man (Lj., extracts AU and A). Insignificant difference in activity was noted between active extracts which had been washed with cold dilute sodium hydroxide and water (A) and those extracts which had not been washed (AU). No sodium-retaining material was recovered from re-extraction of the alkali wash. Since washing with alkali removed much pigment and other material from the extract, and thus facilitated handling and chromatography, this procedure has been followed routinely with all extracts.

TABLE I.—*Effect of pH and of Alkali Wash on Sodium-retaining Activity of Urine Extracts. Effect on K/Na Ratio in μg. D.C.A. Equivalent. Dose=20 Minutes*

Subject	Age and Sex	Diagnosis	Extract at *p*H 6·5 (N)	Extract at *p*H 1 (AU)	Extract AU after Alkali Wash (A)	Extract of Alkali Wash
Ro.	4 M	Nephrosis	0·2	8·1	8·2	−0·9
Jo.	2 M	"	—	8·4	8·3	0
Pe.	4 M	"	—	1·5	0·2	−0·2
Ph.	48 M	Cirrhosis	1·9	—	3·3	—
Lj.	40 M	Normal	−0·8	−0·1	−4·0	−2·3

Activity of Various Extracts in Normal Adults on Usual Diet

Luetscher and Johnson (1954b) found that extracts made by method A from the urine of 11 normal men and women on unrestricted diets either showed no significant sodium-retaining activity or promoted the excretion of sodium in adrenalectomized rats (range +0.5 to −7.2 μg., mean −2.8 μg. D.C.A. per 20 minutes of extract). When such extracts were chromatographed in toluene and propylene glycol, fraction E contained no appreciable activity at doses of 33 minutes. Results of further studies in three of these normal adults are included in Table II. When the dose of "fraction E" of the A extract was increased to 167 minutes there was still no activity (Cases Lj., Ab., and Da.). However, extracts made from the same urine by method B contained strong sodium-retaining activity in fraction E at a dose of 167 minutes. Insignificant activity was found in fraction E prepared from one of these urines after incubation with glucuronidase.

Extracts from Adults on Diets Low in Sodium

It has been reported that when normal men reduced their dietary sodium to 11 mEq a day for five days there was consistently an increase in sodium-retaining activity of the A extracts, but the level reached was not high (Luetscher and Johnson, 1954b). In Lj., on his usual diet (Table II), the activity of the A extract was −4.0 μg., and on a low-sodium diet it rose to +1.4 μg. per 20-minute dose, and significant activity appeared in fraction E. In the extract prepared by method B, five times as much aldosterone was found with salt restriction, for on bioassay the effect produced by a dose of 30 minutes was the same as that produced by a dose of 167 minutes when the subject was on his usual diet. Likewise, on salt restriction, glucuronidase released additional sodium-retaining material (extract AG), which appeared in fraction E on chromatography. Since incubation of urine without glucuronidase at *p*H 4.8 and 37° C. for four hours (extract ACg) did not release appreciable sodium-retaining material, it appears that the addition of glucuronidase was responsible for the observed activity in extract AG. Observations on two other normal men (Cases Ab. and Jb., Table II) resemble those in Case Lj.

Activity of Various Extracts in Heart Failure and Hepatic Cirrhosis

Studies were made on urine of three patients in whom congestive heart failure was associated with a marked reduction of sodium excretion (Table III). In Case Bu., extracts A and B contained far more active material than comparable extracts from normal adults on a similar sodium intake, for in doses of only 20 minutes there was highly significant activity. Glucuronidase (AG) released much additional active material, while a smaller but significant yield was obtained from the control (ACg) incubated without glucuronidase at 37° C. and *p*H 4.8 for 24 hours. When

these extracts were chromatographed, activity was found in fraction E in each instance. In Case Ta., similar results were obtained from extracts A and AG. Case Lo. again demonstrates the appearance of much activity after 24 hours at *p*H 1.

Two patients, We. and Ph., had Laennec's cirrhosis with ascites and impaired excretion of sodium (Table III). In both cases, extracts A and B contained strong activity, which could be found in fraction E after chromatography.

Activity of Extracts in Children

Previous studies of four normal children on unrestricted diets showed insignificant activity in A extracts at doses of 20–33 minutes (Luetscher and Johnson, 1954a). Extracts made by method B contained measurable activity when the dose was increased to 167 minutes. When the three methods of hydrolysis were compared in one case (Rg., Table IV), method B released aldosterone in an amount only slightly less than that found in normal adults, but extracts A and G did not contain amounts measurable in the dosages given.

Three children with oedema due to the nephrotic syndrome were studied (Table IV). The A extracts showed strong activity in two cases, while the third was not significantly active. The B extracts were highly active, and so were the fractions E derived from them. Compared with that from a normal child these B extracts from nephrotic children contained much more aldosterone; for on bioassay the effects of doses of 20 and of 33 minutes were greater than that produced by a dose of 167 minutes from the normal child.

In one case (Co.) the substance responsible for the sodium-retaining activity was isolated from extracts prepared by methods A and B. In each instance a corticosteroid indistinguishable from aldosterone was obtained.

In Case Ro. the fraction E derived from urine incubated with glucuronidase (G) showed strong activity. When this

TABLE II.—*Sodium-Retaining Activity in Various Extracts of Urine from Normal Adults on Usual Diet and on Sodium Restriction*

Subject	Age and Sex	Sodium mEq/day		Method of Hydrolysis	Sodium-retaining Activity µg. D.C.A. Equivalent/Dose	
		Diet	Urine		Extract	Fraction E
Lj.	40 M	Usual	155	Acid (A)	−4·0/20 mins.	0·5/167 mins.
				,, (B)	—	10·3/167 ,,
				Glucuronidase[1] (G)	—	1·9/167 ,,
		11	7	Acid (A)	1·4/20 mins.	2·9/60 ,,
				,, (B)	—	10·5/30 ,,
				Glucuronidase[2] (AG)	5·1/20 mins.	7·0/33 ,,
				,, control (ACg)	−1·9/20 ,,	—
Ab.	28 M	Usual	149	Acid (A)	—	−2·1/167 mins.
				,, (B)	—	6·4/167 ,,
		11	23	,, (A)	—	0·9/130 ,,
				,, (B)	—	7·7/33 ,,
Jb.	31 M	11	2	,, (A)	—	1·6/33 ,,
				Glucuronidase[3] (AG)	—	3·0/33 ,,
Da.	31 F	Usual	74	Acid (A)	—	−0·8/167 ,,
				,, (B)		12·2/167 ,,

[1] Warner-Hudnut 200 units per ml. for 24 hours. [2] Warner-Hudnut 400 units per ml. for 4 hours. [3] Vio-Bin 100 units per ml. for 47 hours.

TABLE III.—*Sodium-Retaining Activity in Extracts of Urine from Patients with Congestive Heart Failure or Hepatic Cirrhosis with Ascites*

Subject	Age and Sex	Diagnosis	Sodium mEq/Day		Method of Hydrolysis	Sodium-retaining Activity µg. D.C.A. Equivalent/Dose	
			Diet	Urine		Extract	Fraction E
Bu.	18 M	Aortic insufficiency	102	4·8	Acid (A)	5·8/20 mins.	4·4/33 mins.
					,, (B)	13·2/20 ,,	10·0/20 ,,
					Glucuronidase[1] (AG)	9·6/20 ,,	6·6/33 ,,
					,, control (ACg)	5·6/20 ,,	4·8/33 ,,
Ta.	41 F	Mitral stenosis	68	1·2	Acid (A)	3·2/20 ,,	3·4/33 ,,
					Glucuronidase[2] (AG)	—	7·4/33 ,,
Lo.	42 M	Aortic stenosis	345	1·8	Acid (A)	—	−2·0/33 ,,
					,, (B)	—	12·6/33 ,,
We.	42 M	Laennec's cirrhosis	85	1·7	,, (A)	8·2/20 mins.	8·2/33 ,,
					,, (B)	—	10·8/33 ,,
Ph.	48 M	,, ,,	51	3·3	,, (A)	3·3/20 mins.	—
					,, (B)	8·0/20 ,,	—

[1] Warner-Hudnut 200 units per ml. for 24 hours. [2] Vio-Bin 85 units per ml. for 69 hours.

TABLE IV.—*Sodium-Retaining Activity in Extracts of Urine from a Normal Child and Three Cases of the Nephrotic Syndrome*

Subject	Age and Sex	Diagnosis	Sodium mEq/Day		Method of Hydrolysis	Sodium-retaining Activity µg. D.C.A. Equivalent/Dose	
			Diet	Urine		Extract	Fraction E
Rg.	4 M	Normal	Usual	49	Acid (A)	0·5/20 mins.	0·8/33 mins.
					,, (B)	—	5·7/167 ,,
					Glucuronidase[1] (G)	—	−0·1/33 ,,
Co.	10 M	Nephrosis	Low	0·8	Acid (A)	8·4/20 mins.	6·3/20 ,,
					,, (B)	10·4/20 ,,	10·8/20 ,,
Ar.	4 M	,,	,,	1·7	,, (A)	1·6/20 ,,	—
					,, (B)	10·3/20 ,,	8·0/33 mins.
Ro.	4 M	,,	,,	0·5	,, (A)	8·2/20 ,,	14·1/33 ,,
					Glucuronidase[3] (AG)	—	15·7/33 ,,
					Glucuronidase[3] (G)	—	5·7/33 ,,
					Acid (A) after (G)	—	13·0/33 ,,

[1] Vio-Bin 100 units per ml. for 48 hours. [2] Vio-Bin 150 units per ml. for 70 hours. [3] Vio-Bin 275 units per ml. for 48 hours.

urine was first extracted after exposure to acid by method A and then incubated with glucuronidase, a very highly active extract was obtained (AG). However, the actual amount of activity in these two glucuronidase extracts cannot be compared, because of the different times of incubation. There were similar amounts of activity in the two "immediate acid" extracts A, and acid A after G, although one was prepared in the usual way and the other after the glucuronidase extract had been made from it. These observations suggest that there are at least two forms of conjugated aldosterone, one form being more readily hydrolysed by acid, and the other by glucuronidase.

Discussion

There are obviously two separate factors which affect the activity of urinary extracts. These are the method of hydrolysis and the amount of active material present in the urine.

Effects of Methods of Hydrolysis on Yield.—In all cases studied, the sodium-retaining activity of the extract increased with time of exposure to strong acid. Negligible activity appeared in extracts of neutral urine. Extracts prepared after 40 minutes at *p*H 1 were more likely to contain active material; while a second extraction after 24 hours' exposure to *p*H 1 regularly produced strongly active material. In one instance incubation at *p*H 4.8 and 37° C. for 24 hours yielded the same amount of activity as brief exposure to *p*H 1 at 20° C. These results parallel the enhanced extraction of glucocorticoids after acidification of urine (Venning *et al.*, 1953). Beta-glucuronidase, prepared from mammalian spleen or liver, released active material in amounts equal to or greater than the initial extract at *p*H 1, but less than the quantity obtained after a day at *p*H 1. Although some of the active material was liberated by the physical conditions rather than by the enzyme, controlled experiments indicate that the beta-glucuronidase was responsible for a part of the yield. These results again resemble the effects of glucuronidase on the release of biologically active glucocorticoids, as described by Venning *et al.* (1953).

Factors Influencing Output in Urine.—The sodium-retaining activity of the various extracts was increased when dietary sodium was reduced or when the presence of disease of the heart, liver, or kidneys was associated with abnormal sodium retention. In all these cases high sodium-retaining activity was associated with low urinary sodium. These findings and other data (Luetscher and Johnson, 1954b) suggest that sodium-retaining activity of urinary extracts reflects the intensity of conservation of sodium by the body; and it appears that the stimulus to conserve sodium can be evoked in health by sodium deprivation, and in some diseases by an as yet ill-defined mechanism.

Identity of Active Material with Aldosterone.—In previous work, cited above, it has been shown that the purified active material obtained from urine in nephrosis has properties identical with those of aldosterone. This finding was confirmed with two extracts from one patient in the present work. In the other subjects, both in health and in disease, the sodium-retaining activity consistently appeared in fraction E on chromatography. Aldosterone is the only known corticosteroid in this fraction which causes sodium retention in the assay used. In several instances fractions have been carried through additional chromatographic systems described by Bush (1952) as B_2, B_5, and C. In each case the active fraction from urine has moved at the same rate as samples of authentic aldosterone, and has shown similar pharmacological properties. For all these reasons it is presumed that the active material is aldosterone in each instance both in normal men and in patients, and when released by brief or prolonged exposure to acid or by glucuronidase.

Summary

The amount of sodium-retaining corticoid that can be extracted from urine by chloroform depends partly on the method of hydrolysis. Of the procedures studied, the greatest yield was obtained from urine after standing for one day at *p*H 1. Smaller quantities were obtained after brief exposure to *p*H 1 or after incubation at 37° C. and *p*H 4.8. Mammalian beta-glucuronidase caused a further release of material. Insignificant activity was found in extracts from urine at *p*H 6.5.

When yields obtained by each method were compared, the sodium-retaining activity of urinary extracts was small but still measurable in health on unrestricted sodium intake. Reduction of dietary sodium was followed by increased sodium-retaining activity. Patients with congestive heart failure, hepatic cirrhosis, or the nephrotic syndrome had a high output of sodium-retaining material when the urinary sodium was low.

In all cases in which urine extracts were chromatographed, sodium-retaining material was found in a single fraction. The active component of this fraction was shown to be aldosterone in one case. It seems highly probable that the sodium-retaining corticoid with similar properties, found in the other cases, was aldosterone.

We wish to thank Anne Dowdy, Julia Harvey, Way Lew, and Lee J. Poo for their invaluable assistance. Dr. C. V. Fisher, of Warner-Chilcott Laboratories, generously supplied purified beta-glucuronidase solution.

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In its first annual report since its incorporation, the British Rheumatic Association describes plans for a study in a London borough "to see how many of the bed-ridden, institutionalized, and chair-bound rheumatic people could be equipped for employment in open industry or for independent living in the community." A grant for this work has been received from a charitable trust, and negotiations are proceeding with the Ministry of Health and the London County Council. Other subjects discussed in the report include the association's hostel (Bracken Hill House) for the investigation of industrial workers thought to be suffering from rheumatism; rehabilitation; and the production of a documentary film to teach patients with rheumatism how to help themselves. Last year the association's total income was £3,646, and a deficit of £720 was incurred on the year's working. However, in view of the great activity and change during the year, the honorary treasurer expressed "every confidence that there was no need to be alarmed about the financial situation."

EFFECT OF METHYLANDROSTENEDIOL ON POST-OPERATIVE LOSS OF WEIGHT

BY

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AND

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The pattern of the metabolic response to surgical trauma is steadily becoming better defined. It is now accepted that in the early post-operative phase there is retention of water and sodium, with an increased excretion of potassium and nitrogen. In a few days there is water and sodium diuresis with potassium retention, and in less than a week normal balance of water and electrolytes is usually restored. The negative nitrogen balance, however, continues for about two weeks, and occasionally for four weeks or longer (Elman, 1940). During this period there is progressive loss in weight. This is masked in the early days by water retention. The eventual total loss in weight is often greater than that calculated from nitrogen-balance studies, and the discrepancy is probably due to oxidation of fat (Moore and Ball, 1952).

The phase of recovery is dependent on an adequate food intake. In the early post-operative phase, however, a high-protein diet and protein hydrolysates are poorly tolerated and poorly utilized (Abbott *et al.*, 1946). They seldom prevent the phase of negative nitrogen balance, and an increase in intake of nitrogen is usually mirrored by an increase in urinary excretion.

Testosterone is well established as a substance that can reduce nitrogen excretion and produce an anabolic phase in normal people and in those suffering from wasting diseases (Abels, Young, and Taylor, 1944). It has also been shown to modify to some extent the catabolic phase after trauma in man and experimental animals, and is sometimes used for this purpose, particularly after burns and in wasted patients.

Methylandrostenediol is a synthetic hormone, effective by mouth. It has been shown to have a nitrogen-conserving effect equal to testosterone but only about a tenth of its virilizing effect (Gordon *et al.*, 1951). Some reports do suggest, however, that it is quantitatively less potent than testosterone (Henderson and Weinberg, 1951). It has become a fairly popular medicament in a variety of wasting conditions and many authors claim that it is effective—for example, Albeaux-Fernet *et al.* (1952). The present study was designed to measure its effect on the loss of weight which follows operation.

Investigation

The patients in the trial were suffering from pulmonary tuberculosis. Because the metabolic response is quantitatively less in people whose tissues are already depleted, only young adults in a good state of nutrition and free from clinical evidence of toxaemia were chosen for study. Those with obesity and diabetes mellitus were not included. Patients who subsequently developed wound infection or pleural effusions requiring aspiration were excluded from the final analysis.

As the metabolic disturbance is also proportional to the extent of surgical trauma, the fairly standardized operations of thoracoplasty, extrapleural plombage, lobectomy, and combinations of these provided suitable cases for study.

Patients were weighed on the day before operation and twice weekly afterwards for a minimum of six weeks. The weighing was done at the same time of day and in the same garments. The patients were allocated by random sampling to the treatment or control group. Those in the treatment group were given 20 mg. of methylandrostenediol twice daily, starting on the day before operation and continuing for twenty-one days afterwards. In those undergoing operation in two stages the interval between the first and second varied, but was usually fourteen days. In the latter cases treatment was continued from the day before the first operation until twenty-one days after the second.

The patients remained on ordinary hospital diet throughout. Post-operative vomiting was uncommon, and patients operated on in the morning were often able to eat a boiled egg and bread-and-butter at tea-time.

Results

In patients undergoing one operation, 20 were treated with methylandrostenediol and 14 formed the control group. The groups were comparable in sex, age, and type of operation. The findings are summarized in Table I. In the treatment group the maximum weight loss varied from nil to 9 lb. (4.1 kg.), averaging 4.3 lb. (1.9 kg.). In the control group the range was 2 lb. (0.9 kg.) to 9.5 lb. (4.3 kg.), with an average of 4.8 lb. (2.1 kg.). The time of maximal weight loss was comparable in both groups.

In those undergoing two operations, 12 patients formed the treatment group and 15 the control group (Table II). Again the groups proved comparable. In the treated group one patient lost no weight, but the others lost amounts varying from 4.5 (2 kg.) to 14 lb. (6.4 kg.), the average for the group being 8.9 lb. (4.1 kg.). In the control group the loss varied from 4 (1.8 kg.) to 15.5 lb. (7 kg.), with an average of 8.7 lb. (4 kg.).

Thus there is no evidence that methylandrostenediol in the dose used has any significant effect on post-operative weight loss. No harmful effects could be attributed to its use and there was no evidence of virilization in the female patients.

Discussion

The tables show that the loss in weight after major surgery is considerable, and in some three-stage procedures studied (unpublished) it frequently exceeds 14 lb. (6.4 kg.) in people of average nourishment. The return to pre-operative weight often takes three months, and is sometimes never reached. It is generally agreed that one of the major factors in producing resistance to tuberculosis is a diet adequate in protein. Short of obesity, there is an intimate and progressive relation between gain in weight and the success and eventual result of treatment. The considerable loss of weight

TABLE I.—*One-stage Operation*

Treated			Control		
Maximum Weight Loss lb.	kg.	Day of Maximum Loss	Maximum Weight Loss lb.	kg.	Day of Maximum Loss
3	1·4	11	7·5	3·4	25
2	0·9	18	4	1·8	25
3·5	1·6	28	5	2·3	18
3	1·4	18	2	0·9	11
4·5	2·0	25	8	3·6	35
8	3·6	28	3	1·4	18
0	0	—	4·5	2·0	23
9	4·1	35	4·5	2·0	14
5	2·3	25	4	1·8	14
6	2·7	18	5	2·3	28
1·5	0·7	21	4	1·8	7
3·5	1·6	11	2·5	1·1	14
5	2·3	21	4	1·8	11
8·5	3·9	49	9·5	4·3	14
4	1·8	11			
1·5	0·7	11			
3	1·4	7			
5	2·3	21			
4·5	2·0	7			
5·5	2·5	35			
Average 4·3	1·9	20	4·8	2·2	18

TABLE II.—*Two-stage Operations*

Treated			Control		
Maximum Weight Loss lb.	kg.	Day of Maximum Loss*	Maximum Weight Loss lb.	kg.	Day of Maximum Loss*
7	3·2	32	13	5·9	18
4·5	2·0	11	8·5	3·9	18
0	0	—	7	3·2	18
11	5·0	11	5·5	2·5	14
9·5	4·3	35	9·5	4·3	21
12·5	5·7	21	7	3·2	35
12	5·4	17	4	1·8	32
14	6·4	30	6	2·7	18
5·5	2·5	11	8	3·6	18
12	5·4	21	10	4·5	11
6	2·7	7	10	4·5	32
12·5	5·7	28	8	3·6	21
			12	5·4	14
			15·5	7·0	22
			7	3·2	56
Average 8·9	4·0	19	8·7	3·9	20

* Day after second stage operation.

is therefore an unwelcome feature of the post-operative phase, and its presence may well exert an unfavourable effect on the eventual course of the disease. Methylandrostenediol has proved disappointing in its effect.

We have made no attempt at direct measurement of nitrogen balance in this investigation. Even though part of the weight loss may be due to oxidation of fat, it is reasonable to attribute most of it to nitrogen loss. It seems justifiable to assess the efficiency of an anabolic hormone in the post-operative phase by the method we have used. We feel that only when a drug can be shown to influence the weight pattern can it be regarded as effective therapy. Our results do not indicate that methylandrostenediol has no effect on nitrogen metabolism, but only that its effects are not strong enough to be apparent clinically. It remains a possibility that a fivefold increase in dose might have some measurable effect, but at this level its virilizing effect, too, would be apparent, particularly in women treated for five weeks or longer. In most reports to date, the dosage has been in the range that we have used.

Summary

The pattern of the metabolic response after surgical trauma has been described briefly.

The considerable loss of weight that takes place after operation is an undesirable feature. This is particularly so in tuberculous patients undergoing multiple operations on the chest.

Methylandrostenediol has not been found to reduce this weight loss.

We have to thank many of the medical staff at Harefield Hospital for helping us in this investigation, particularly Drs. R. S. Francis, D. Levy, and R. G. May. We are grateful to the nursing staff for undertaking the extra work so willingly.

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RAPID Rh-TYPING

A "SANDWICH" TECHNIQUE

BY

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It is necessary to perform ABO and Rh blood-grouping tests before transfusion, and recipients who are Rh-negative should be transfused with Rh-negative blood of homologous ABO group.

Blood banks are usually short of Rh-negative blood of all ABO groups and it is sometimes necessary, in the first instance, to transfuse males who have never had any previous blood transfusion, or intramuscular injections of blood, with Rh-positive blood because of such shortage. This applies only to males and to their first visit to hospital, and such a transfusion should not be continued for more than a few days in succession, nor is it desirable that Rh-positive blood should be given to Rh-negative males who will obviously require multiple transfusions. I have seen Rh antibodies produced in an Rh-negative male patient seven days after primary transfusions of Rh-positive blood.

In the case of females, all those who are Rh-negative, of whatever age, should be transfused with Rh-negative blood. It is not generally appreciated that children who are Rh-negative can be immunized as easily as adults. I have seen an Rh-negative child, 5 years old, immunized by transfusions of Rh-positive blood. Once Rh antibodies have appeared in the blood of Rh-negative females they persist for long periods of time, probably for life. In another case recently observed, Rh antibodies were present in a woman aged 73 who had never received any blood transfusions or intramuscular injections of blood and whose last pregnancy was 38 years previously.

ABO typing can be rapidly and reliably performed, but with the Rh-typing sera available the recommended techniques often take a long time, and when a cross-matching test has to be done in addition to this there may be delay before the blood can be given. Consequently some transfusions, in the minds of clinicians, become "emergency transfusions," and they take the risk of giving blood without the necessary preliminary grouping and cross-matching tests being performed. If the period of time required for the preliminary grouping tests could be reduced then perhaps fewer transfusions would be regarded as being of an emergency nature.

The purpose of this paper is to describe a rapid method of Rh-typing which can be performed on a slide in ten minutes, using Rh-typing sera ordinarily available here.

Materials and Methods

Bovine Albumin.—Armour's 30% bovine albumin and bovine plasma have both been used in this test.

Rh-Typing Serum.—Undiluted anti-Rh serum is used, suitably absorbed to remove anti-A and anti-B agglutinins so that it is universally applicable. The sera employed had been kept frozen solid for several weeks. Strengths of the reaction of a typical serum used in this test are shown in the Table.

Red-Cell Suspensions.—The blood samples are collected either as clotted or as citrated blood. If collected as clotted

Titration of Serum 474, *Using Group O, R_1R_2 Test Cells*

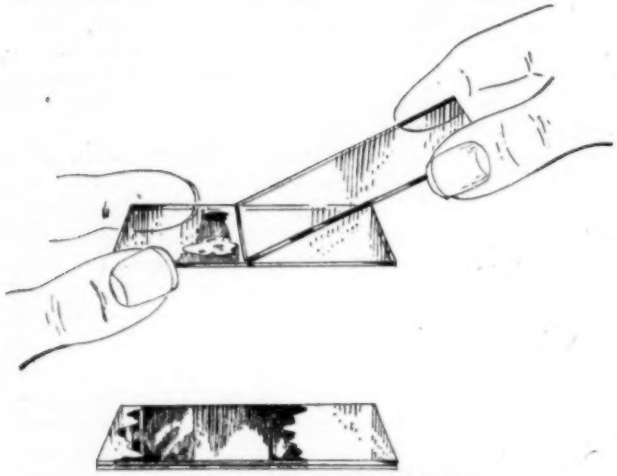
Diluting Fluid	Dilutions of Serum									Control
	1:1	1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	
Saline	—	—	—	—	—	—	—	—	—	—
20% albumin ..	++++	+++	++	+	—	—	—	—	—	—

blood, the cell-serum mixture is poured or pipetted off the clot. Citrated or clotted cells are then spun and the serum or plasma is removed. The cells that remain are then washed once in a large volume of saline and packed tightly in the centrifuge. The supernatant saline is then completely removed from the cell pack with a pipette.

Methods.—The saline tube agglutination and albumin tube agglutination techniques were performed according to standard methods (M.R.C., 1952).

Technique

One volume, about 0.03 ml., of the Rh test serum, together with one volume of the 30% bovine albumin and one volume of the packed cells to be typed, is placed in the middle of a microscope slide. The human anti-Rh serum and the 30% bovine albumin may be mixed in equal volumes prior to the test, and two volumes of the mixture used together with one volume of washed packed red cells. The volumes are delivered on to the microscope slide by using a marked Pasteur pipette. On the right-hand side of the slide the



Preparation of the "sandwich."

reference number of the cells that are being typed is marked in grease pencil. The slide is then held in the left hand and another microscope slide held by the narrow edge with the thumb and first finger of the right hand, and the serum albumin and packed red cells are mixed together with the narrow edge of the slide, as in making a blood film. The mixture is spread out on the slide for two-thirds of its length. The slide with which the mixing was done is then gently lowered and pushed on top of the bottom slide so that a "sandwich" is made and the albumin–Rh-serum–packed-cell mixture is spread out in a thin layer between the two slides (see Fig.). When the "sandwich" is made the slides should not be pushed tightly, but only gently, together. Any excess liquid is gently wiped away from the edges of the "sandwich."

Control tests are put up consisting of group AB serum, 30% bovine albumin, and the patient's packed cells, and the sandwich is prepared as described previously. The sandwiches are then carefully placed on a heated plate or in the incubator at 37° C. They are left for ten minutes, removed, and read, using the low power of the microscope. Several fields in the centre of the slide should be examined. If the result is positive, large clumps of cells will be seen, and if the result is negative the cells will be freely suspended. It is always desirable to examine a moving film, and the thumb of one hand is pressed on top of the sandwich as it rests on the stage of the microscope. As the sandwich is compressed the cells will be observed to move either as clumps in the case of a positive result or as cells which are freely mobile and not aggregated or clumped in a negative one.

Results

One thousand red-cell samples were tested by the tube technique at 37° C., using an anti-D saline agglutinating serum. The results which were negative with this serum were tested with another anti-D serum and also with anti-C and anti-E sera; D^u positive cells were identified and suitable control tests were included.

The 1,000 blood samples were thus divided into D-positive types (including D^u) and D-negative types. These blood samples were then tested by the slide-sandwich technique described above, using anti-Rh serum No. 474, details of the titration of which are shown in the Table. The results were as follows: There were 851 D-positive bloods—847 were typed as positive, 2 as doubtful, and 2 as negative. The remaining 149 were D-negative and all gave negative results using the sandwich technique. The two cells which gave negative results and the two which gave doubtful results, using the rapid sandwich test, were all of variety D^u—either cD^uE/cde or CD^ue/cde.

Forty-two blood samples were also tested by the tube techniques detailed above and also by the sandwich technique, using five different anti-Rh sera (similar to No. 474) on each cell sample; the results were all in agreement. In order to determine whether cells which had been stored in A.C.D. mixture in a refrigerator could be typed by this method, one of these anti-Rh sera (No. 412) was used to test blood samples from outdated stored blood (average age, 21 days). Of 100 blood samples examined, 83 were D-positive and 17 D-negative, using the routine tube techniques, and identical results were given by the sandwich slide technique.

Discussion

Diamond and Denton (1945) introduced bovine albumin for the detection of incomplete Rh antibodies, and subsequently Diamond and Abelson (1945) introduced the open-slide test, using albumin for rapid Rh-typing. This test has been used in many laboratories and has been found to give satisfactory results, but for its success it is necessary to have an avid Rh-typing serum and to have considerable experience in the performance of the test. Such avid Rh-typing sera may mean reimmunizing human volunteers whose sera already contain Rh antibodies with injections of Rh-positive red cells. Such sera are not always available in this country. Another difficulty encountered during the performance of this test is the fact that the cell–serum–albumin mixture on the open slide tends to dry up towards the end of the test, making it difficult on occasion to read it. Furthermore, if people are not familiar with the methods of performing these tests, and if weak or low titre Rh antisera are used, a number of false-negative results occasionally occur, Rh-positive cells (often of type R_1r) being falsely diagnosed as Rh-negative.

Because of the need for a rapid slide test, the sandwich method was developed; it has a number of advantages. First, there is no trouble with drying up of the serum-albumin mixture, since although the mixture dries at the edges of the slides the mixture in the centre of the sandwich remains quite fluid. The drying of the edges is, in some respects, an advantage, since the sandwich becomes very stable, and even though dropped on the bench the slides will not come apart, and the patient's name or number cannot accidentally be rubbed off, as it is in the middle of the sandwich. Secondly, the anti-Rh sera that can be successfully used with the sandwich technique are readily available and need not be specially avid or hyperimmune. The test, furthermore, can be performed rapidly, and results were obtained at 37° C. in ten minutes.

It should be emphasized that the test is specifically designed for rapid Rh-typing before blood transfusion, and it

is not intended to be used as a routine typing method. A number of false-negative results were obtained, but these were all of the D^u variety of Rh, which are known not to be detected by the albumin technique (Renton and Stratton, 1950).

In using this test for the purpose for which it was designed, occasional false-negative results will not cause difficulty. False-positive results were not detected in the tests that were made. False-positive results do rarely occur in special circumstances—for example, in a recent case in which the cells from an Rh-negative patient suffering from acquired haemolytic anaemia were typed, they were found to be positive, but, similarly, the cells gave clumps when AB serum was substituted, as suggested in the technique, and used as a control. This false-positive result, therefore, was readily detected. Occasionally, slight rouleaux formation was observed, but this slight aggregation of cells is rapidly dispersed on compressing the slide and watching the cells under the microscope. A similar dispersal of cells does not so readily occur in the case of true agglutinates. No serious trouble was encountered in the interpretation of the results due to the presence of rouleaux formation. In avoiding rouleaux formation, care must be taken to see that the cell suspensions are washed properly, and, furthermore, that when the albumin–cell mixture is made on the slide it is not allowed to dry at all before the sandwich is made. An additional precaution is to avoid reading the edges of the sandwich. It is assumed, of course, that the Rh-typing serum has no rouleaux-forming properties, and it is often an advantage to keep these sera frozen solid for a week or two before bringing them into routine use. The bovine albumin should also be a reliable and non-rouleaux-forming batch.

If strong anti-D + D^u typing sera are used then some of the high-grade types of D^u can be detected, using the sandwich technique. One of the objects in employing this test, however, as stated previously, was to make it useful with weaker Rh-typing sera and with Rh-typing sera containing incomplete Rh antibodies, which would not normally be used for the saline agglutination test performed in tubes at 37° C.

Summary

In order to shorten the period of time required for the performance of the compatibility test, rapid methods for ABO and Rh typing are necessary. This paper describes a slide sandwich test for rapid Rh typing.

This test is intended to be used prior to blood transfusion and can be performed in ten minutes at 37° C.; it is not intended for routine use when large numbers of specimens have to be tested.

In this technique anti-Rh sera of moderate titre and avidity, such as are ordinarily available in this country, can be employed.

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In his annual report for 1953 Dr. V. Freeman, medical officer of health of Islington, refers once again to housing conditions in the borough. With an average of 76.2 persons to the acre it is one of the most densely populated boroughs in the county of London. Many of Islington's houses are out of date, being in the form of multi-story tenements, built during the early part of Queen Victoria's reign, or even earlier. Of the 82,000 private households in the borough, 53% share a water closet with other households, 42% share a piped water supply, 22% share a kitchen sink, 20% share a fixed bath, and 7% share a cooking stove. No fewer than 59% of the households are without a fixed bath. Many Islington houses are structurally sound, but it is uneconomic for the landlords to keep them in repair owing to the high cost of labour and materials.

A SIMPLE METHOD OF Rh-TYPING

BY

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It is generally accepted that the most reliable method of Rh-typing is that of Landsteiner and Weiner (1941), in which a suspension of red cells is incubated for two hours with an equal volume of anti-D serum in a small tube, the results being read microscopically. This method is too lengthy in cases in which blood is urgently needed, and shorter methods have been used.

The capillary-tube method originally described by Chown (1944) has been widely used, and yields results within thirty minutes. However, Poole and Williams (1951) have reported false-positive readings with this technique, and Chown and Lewis (1951) have advised that the cells should be washed for use in this test.

Poole and Williams (1951) have reported good results with a technique in which the cells and anti-D serum were first incubated at 37° C. for ten minutes and then centrifuged for five minutes at 2,000 to 2,500 r.p.m.

A modification of this technique (F. Stratton, 1952, personal communication) is called the double incubation and centrifuging method. The tubes of cells and serum are incubated and centrifuged, tapped to resuspend the cells, and then reincubated and centrifuged. This technique has been recommended by the Manchester Regional Hospital Board Advisory Committee on Pathology for use in emergencies. By this means, results can be obtained in about fifteen to twenty minutes. The method has the drawback of repeated manipulations, and it was thought that the number of manœuvres could be reduced if the centrifuge itself were heated to 37° C., thus acting as an incubator. It was hoped that this short and simple method, the "thermal centrifuging method," would yield results comparable to the standard two-hour incubation method.

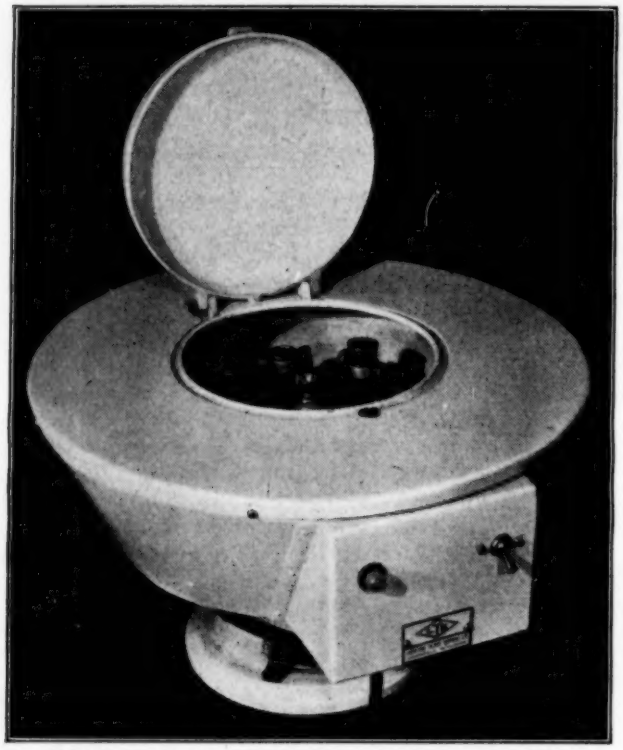
Material and Methods

The cases were routine requests received in the laboratory of a general hospital. They consisted of a small number of midwifery cases undergoing routine typing and some emergency cases received in the casualty department, but the majority were composed of general medical and surgical cases admitted from the waiting-list.

Centrifuge.—This was constructed specially for these experiments by Laboratory Thermal Equipment, Ltd., of Greenfield, near Oldham, Lancs. It consisted essentially of an M.S.E. minor centrifuge, round the outer casing of which a lagged jacket was built, and between this and the casing a thermostatically controlled electrical heating element was fitted (see photograph). No special head was provided, the normal cups being satisfactory for the test. The tubes are removed from the centrifuge cups with forceps.

Cell Suspensions.—The addition of one or two drops of the patient's blood to 2 ml. of saline gives a suspension of approximately 2%. The final concentration of the test is therefore about 1% red cells.

Anti-D Serum.—For use during Experiment 1, special serum of average titre was supplied by the regional transfusion centre and used in all 64 cases. For the other experiments the routine sera supplied by the regional transfusion centre was used, and the titre of these varied. The same serum was used for all the tests made on any cell suspension. Each batch of serum was tested with known Rh-positive and Rh-negative cells.



Centrifuge with thermostatically controlled heating jacket.

Size of Tubes.—Two sizes of tubes have been used and found to be equally satisfactory for the test. These are Dreyer's tubes and Durham's tubes, the latter measuring 5 by 0.4 cm. All tubes were boiled in chromate after each test and then washed repeatedly in water and distilled water. However, Dreyer's tubes are recommended because they are easier to clean. During Experiment 1 the tubes were warmed before use in the 37° C. incubator.

Technique

In all the techniques two tubes were used for each experiment. Both tubes contained one drop of a suspension of the patient's cells. In the first tube a drop of anti-D serum was added, and in the other a drop of normal saline. This second tube was used as a control.

Standard Two-hour Method.—The pair of tubes were placed in adjacent holes, drilled in the top of a wooden block, and the block was placed in the 37° C. incubator. After two hours the block was removed from the incubator and the tubes were examined for macroscopic agglutination. The contents of both tubes were then gently pipetted on to clean slides and read under the 2/3 objective of a microscope with reduced light. The slide was tipped slowly from side to side to facilitate the recognition of agglutination in difficult cases. This method of reading the results was followed in all the techniques. The standard two-hour method is referred to as the "standard" method.

Double Incubation and Centrifuging Method.—A modification of Stratton's technique was used. The two tubes were incubated in the 37° C. incubator for seven to fifteen minutes, then centrifuged at about 500 r.p.m. for one minute, tapped to resuspend the cells, reincubated for seven to fifteen minutes, recentrifuged, and then read. This method is referred to as the "rapid" method.

Thermal Centrifuging Method.—The two tubes were dropped into opposing cups of the special centrifuge and spun in all experiments at 100–150 r.p.m. The duration of the centrifuging varied as follows: in Experiment 1, fifteen minutes; in Experiment 2, twenty minutes; in Experiment 3, thirty minutes. At the end of the centrifuging the tubes were removed from the cups and read immediately. This method is referred to as the "centrifuging" method.

The degree of agglutination was estimated by the following scale under the microscope. 0=No agglutination. 1=Occasional agglutination of two, three, or four cells. 2=A considerable number of cells agglutinated—that is, clumps up to six or eight cells. 3=Practically all cells agglutinated. Clumps of up to a dozen cells or so. 4=Large aggregates visible with the microscope or naked eye on the slide. 5=Agglutination visible with the naked eye in the tube.

Results

Experiment 1.—Sixty-four cases were tested. The methods used were the standard method and the centrifuging method, spinning for fifteen minutes. Fifty cases were Rh-positive by the standard method, and the figures denoting the degree of agglutination were added together so that the intensity of the agglutination by both the techniques could be compared over the whole 50 cases. The results are shown in Table I. There were no false positives or false negatives.

TABLE I.—*Experiment* 1 (64 *Cases:* 50 *Rh-positive,* 14 *Rh-negative*)

Method	Total Pos.	Total Aggregate of Agglutinations	False Pos.	False Neg.	First-degree Agglutinations	False Neg.+Weak Pos.
2-hour standard	50	174	0	—	5	5
15-minutes centrifuging ..	50	162	0	0	6	6

Experiment 2.—In this experiment 135 cases were tested and the following methods were compared: the standard method; the rapid method, using two ten-minute periods of incubation; and the centrifuging method, spinning for twenty minutes. As it was felt that the first degree of agglutination should be listed separately, such results were called "weak positives." The results are set out in Table II. There were no false positives.

TABLE II.—*Experiment* 2 (135 *Cases:* 113 *Rh-positive,* 22 *Rh-negative*)

Method	Pos.	Neg.	Weak Pos.	False Pos.	False Neg.	False Neg.+Weak Pos.	Total
2-hour standard ..	112	22	1	—	—	1	135
2×10-minutes rapid	102	24	7	0	2	9	135
20-minutes centrifuging	107	23	4	0	1	5	135

Experiment 3.—In this experiment the following methods were compared: the standard method; the rapid method, using two fifteen-minute periods of incubation; and the centrifuging method, spinning for thirty minutes. The results are set out in Table III. It will be noted that there are no false positives.

TABLE III.—*Experiment* 3 (50 *Cases:* 37 *Rh-positive,* 13 *Rh-negative*)

Method	Pos.	Neg.	Weak Pos.	False Pos.	False Neg.	Weak Pos.+False Neg.
2-hour standard ..	37	13	0	—	—	0
2×15-minutes rapid	35	13	2	0	0	2
30-minutes centrifuging	37	13	0	0	0	0

Discussion

The results of Experiment 1 show that with the fifteen-minutes centrifuging technique the aggregate of agglutinations is close to that obtained by the standard technique and there are no false negatives.

While these results show what can be achieved in the hands of experienced workers, a technique for use in emergency cases must be capable of giving satisfactory results when used by people who practise it infrequently. It was

felt that the first degree of agglutination might be too subtle for comparatively inexperienced personnel to recognize, and such results are therefore listed separately as "weak positives" in subsequent experiments. Thus, in Experiments 2 and 3, three results were possible in each experiment—"negative," "weak positive," and "positive."

The most suitable technique would be that in which there is the smallest number of false negatives and weak positives as compared with the standard method.

In Experiment 2 the centrifuging method was used for twenty minutes, as it was hoped that by lengthening the period of spinning the number of one-plus agglutinations would be reduced. It was also compared with the rapid method with two separate incubation periods of ten minutes each. This rapid method is often used in emergencies for Rh-typing, but inexperienced personnel complain of the numerous manipulations involved.

The results show that in 113 Rh-positive cases tested, the total of one-plus agglutinations plus false negatives was five for the twenty-minutes centrifuging and nine for the two ten-minutes rapid method, as compared with one in the standard technique. Thus the superiority of the twenty-minutes centrifuging method as compared with the two ten-minutes rapid method is established, the results being slightly better and the technique easier to carry out.

The results obtained by any Rh technique must depend upon the avidity of the Rh-typing serum supplied. One batch used in Experiment 2 was weaker than the rest, and it was while this was being used that a case was tested which gave a weak positive by the standard and false negatives with both the rapid and the centrifuging techniques.

In Experiments 1 and 2 no false positives were encountered—an important point in emergency Rh-typing.

Experiment 3 was carried out to compare the efficiency of the centrifuging technique with the rapid method when they were both used for a longer period, and also to find out if false positives occurred then. No false positives were encountered, and the efficiency of the centrifuging technique in the small series tested was found to be comparable with that of the standard method.

Summary and Conclusions

A new technique is described in which Rh-typing is carried out by spinning a suspension of the patient's cells with anti-D serum in a centrifuge heated to 37° C. by a thermostatically controlled jacket.

The twenty-minutes centrifuging method gives almost as reliable results as the standard two-hour method, with no false positives. It gives slightly better results than the two ten-minutes rapid method, and, since there are fewer manipulations, it is recommended as a procedure to be adopted in emergency Rh-typing.

I am indebted to Dr. James Davson for advice and encouragement, to Dr. F. Stratton, the director of the Manchester Regional Blood Transfusion Service, for reading the paper and for criticism, and also for supplying the special serum used in Experiment 1.

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The *Bethlem Maudsley Hospital Gazette*, published quarterly, is a lively and entertaining journal produced for and by the staff of the Bethlem Royal Hospital and the Maudsley Hospital. The issue which came out at the end of last year contains all the usual features of a weekly professional journal, including editorials, letters to the editor, book reviews, reports of meetings, signed articles, and items of news about the hospital, and also reprints Professor Aubrey Lewis's Maudsley Lecture entitled "Henry Maudsley: his work and influence."

A FOREIGN BODY IN THE KIDNEY

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The following case is of interest because of the diagnostic confusion it caused and its unusual outcome.

Case Report

A boy of 3½ years was admitted to the Duchess of York Hospital for Babies, Manchester, on January 25, 1954. The history obtained at the time of admission was that he had been well until a month before, when he became listless and developed painful enlarged glands in his neck. Shortly afterwards his left ear began to discharge; this persisted until the time of admission. A week after the cervical adenitis developed his urine became dark. There was no dysuria, but he started to pass urine twice during the night. About the time his urine became dark puffiness of the eyes was noted. This decreased during the interval prior to admission. For two weeks before admission he had vomited occasionally. His appetite, usually good, had become poor and he had become fretful. The only relevant previous history was an admission to another hospital at the age of 1 year for repair of an inguinal hernia. Examination showed a well-nourished, lively, but rather fractious child, with slight puffiness under the eyes. There was no oedema elsewhere. The left external auditory canal was full of thick pus and there were moderately large glands palpable in the neck. No other abnormal signs were found. In view of the history a diagnosis of acute nephritis following an upper respiratory infection was made.

The urine contained albumin and many red cells but no casts. Blood urea was 55 mg. per 100 ml.; E.S.R., 70 mm. fall in first hour; haemoglobin, 56% (Sahli); white cell count, 12,400 per c.mm. (neutrophils 61%, lymphocytes 37%, monocytes 1%, Türk cells 1%); platelet count, 450,000 per c.mm.

The profuse haematuria persisted, but no casts were seen at any time. The urine output was good and the general condition satisfactory. After two weeks there was little change in his condition, and the diagnosis of nephritis was considered to be untenable. At this time the blood urea was 42 mg. per 100 ml.; E.S.R., 20 mm. fall in first hour; haemoglobin, 66%; white cells, 15,000 (neutrophils 54%, lymphocytes 41%, monocytes 1%, eosinophils 4%). The left ear was dry and the drum healed.

As the first step in a full investigation of the renal tract a straight *x*-ray film of the abdomen was taken. This showed a foreign body in the right upper abdomen. A barium meal showed that this body was in close relation to the duodenum, and an intravenous pyelogram indicated that it was also in close proximity to the right renal pelvis (see Fig.).

Operation was performed on February 16 under general anaesthesia. An incision was made in the line of the right twelfth rib, the anterior half of which was removed. The perinephric fascia was opened and the kidney mobilized. The upper half of the kidney was friable and swollen, and had a dark-red mottled appearance. It was very adherent to the surrounding tissues. The duodenum was firmly stuck to the anterior surface of the pelvis of the kidney. The foreign body could be felt passing from the duodenum into the upper part of the kidney. By careful dissection the

duodenum was separated from the kidney except at the site of the short fistulous track through which the foreign body could be felt to be passing. The fistula was divided round the foreign body, which was disengaged from the duodenum with a little difficulty because of the splayed-out ends, which were really broader than the diameter of the duodenal end of the fistula. It was then easily withdrawn from the kidney. No urine leaked from the sinus in the kidney, the external end of which was situated on the edge of the renal sinus just beyond its junction with the pelvis. It appeared to be of kidney substance only and to have no direct connexion

Radiograph showing relationship of foreign body to renal pelvis and duodenum.

with the caliceal system. A piece of perinephric fat was sutured over it. The small opening into the duodenum was closed with two layers of fine catgut and the wound closed in layers, a rubber drain being left to the perinephric space.

The foreign body was identified as a hair-grip of the type known as a "kirbigrip," which was 4.8 cm. long and showed some evidence of erosion of the surface. Microscopical examination of a small piece of the upper pole of the kidney which was removed showed gross interstitial haemorrhage.

The patient made excellent progress after operation and was discharged home three weeks later. Microscopic haematuria persisted for three months after discharge, but the number of red cells in the urine has shown a progressive decrease and they have now become very scanty. At the time of writing the blood urea was 32 mg. per 100 ml. and the child was very active and in excellent health.

The parents were interviewed when the foreign body was discovered, and they remembered that about four months before admission the child had announced one day that he had swallowed a hair-grip. When told he would have to go to the doctor he promptly denied having swallowed anything, and maintained this denial in the face of repeated questioning. Since he appeared perfectly well in the next few days the matter was forgotten. Two months later he had an unexplained illness in which he became listless and anorexic but had no local symptoms. He was examined several times by his own doctor, who found nothing to account for his illness, and after a week he resumed his usual robust health. From about this time his urine was noticed to be cloudy, but it did not become red until three weeks before admission to hospital.

Discussion

The remarkable feature of this case is the behaviour of the foreign body. It had become impacted in the duodenum, and the sharp ends had become firmly fixed against the medial wall of the bowel. Thereupon the rounded end slowly worked its way through the lateral wall and entered the kidney. This whole process was completely silent—unless the vague unexplained malaise two months after the hair-grip was swallowed was to be attributed to it—and finally the child came to hospital presenting the picture of an acute nephritis. He had lost a considerable amount of blood from his renal tract, since his haemoglobin at the time of admission was only 55%.

The varieties of size and shape of foreign bodies which have successfully negotiated the alimentary tract are legion. As a general rule, those which traverse the oesophagus can be expelled per vias naturales. Thus Gross (1953) reported that only 43 of 615 to reach the stomach had to be removed by operation.

We have been able to find reports of four other cases in which swallowed foreign bodies have perforated the bowel quite silently and entered the kidney. All four were young children, and in all of them the symptoms were predominantly renal. The Table gives the relevant data on the five cases now on record.

Details of Five Recorded Cases

Case	Age in Years	Sex	Foreign Body	Symptoms	Duration of Symptoms (Months)	Operation
Capon and Wells (1938)	4	F	Kirbigrip	Frequency; haematuria	7	Nephrectomy
McEnery and Fox (1946)	2	M	Bobby pin	Fever; vomiting; haematuria; pyuria	7	Removal through duodenum
Mackby (1948)	3	F	„ „	Frequency; cloudy urine; fever	6	„ „
Bilger and Greiner (1949)	5	M	Hair-grip	Pyuria	4	Nephrectomy
Present case	3½	M	Kirbigrip	Haematuria; malaise; vomiting	1	Removal without opening duodenum

A bobby pin is the American equivalent of a kirbigrip. The child reported by Capon and Wells was known to have swallowed a hair-grip several months before the onset of symptoms. In none of the other cases was such an incident reported. The two American cases and the other British case are practically identical with ours. In all four the open end of the hair-grip had become stuck in the second part of the duodenum and the rounded end had perforated the wall and entered the kidney. In the French case the foreign body passed as far as the large bowel before being arrested.

These cases are so similar, and the sequence of events so remarkably alike, that we suggest that this be regarded as a definite syndrome. Toddlers are notoriously apt to put things in their mouths, and in the investigation of obscure symptoms in children of this age the possibility of a foreign body as the cause should always be borne in mind.

Summary

A boy of 3½ years developed profuse haematuria three months after swallowing a hair-grip. This was found to be due to arrest of the foreign body in the duodenum and penetration of the right kidney. The foreign body was removed at operation and complete recovery ensued. Four other cases in whom a similar sequence of events occurred are referred to.

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Medical Memoranda

Pyrimethamine in the Prophylaxis of Malaria

Therapeutic trials with pyrimethamine ("daraprim") have indicated that the drug could effectively control a clinical attack of vivax or malariae infection in two to three days but might fail in a certain percentage of falciparum infection (Chakravarty and Chaudhuri, 1953). The present report on the prophylactic value of the drug is based on another investigation carried out simultaneously in a malarious village.

MATERIAL AND METHOD

The prophylactic trial was carried out on 311 boys in a village school about 35 miles from Calcutta from July to November, which is usually the heaviest transmission period in the locality. A preliminary survey was done to find out the spleen and parasite rates; it showed that 60% of malarial infection was due to *P. falciparum* and the rest to *P. vivax* or *P. malariae*. During the course of treatment the blood was examined every month except October, and on its conclusion a final estimate was made of the spleen and parasite rates (see Table). Alternate classes received pyrimethamine (172 boys) and dummy tablets (139 boys) respectively, the latter serving as control. Both were given once a week, the dose of pyrimethamine being 25 mg. (12.5 mg. for boys under 10 years). The tablets were administered personally by a member of the clinical research unit, financed by the Indian Council of Medical Research, except for four weeks during the October vacation, when they were handed over to the boys to be taken by themselves in their homes.

RESULTS

The effect of prophylactic regimen on the parasite and spleen rates is shown in the Table.

Effect of Pyrimethamine Prophylaxis on Parasite and Spleen Rate per 100

Group		July	Aug.	Sept.	Oct.	Nov.	Dec.
Pyrimethamine (172 boys)	Parasite	5·7	0	1·2	—	0·7	2·3
	Spleen	16·1	—	—	—	—	11·6
Control (139 boys)	Parasite	3·6	3·7	8·6	—	6·6	9·2
	Spleen	16·2	—	—	—	—	23·9

The parasite rate in the control group rose, as was to be expected, from 3.6 in July to 6.6 in November, while in the treated group it dropped from 5.7 to 0.7 during the same period. In December, after the conclusion of the experiment, there was an unexpected rise in the parasite rate, which might perhaps have been due to prolongation of the transmission period. The suppressive effect of pyrimethamine was also reflected on the spleen rate, which showed some reduction, while there was about 50% increase in the control group. In all the parasite-positive cases in the treated group only *P. falciparum* was seen throughout the period.

The incidence of overt malaria could not be accurately recorded, as it was not possible to examine the blood during febrile attacks. However, on inquiry at the weekly visits it was gathered that the incidence of fever was much less in the treated group.

COMMENT

Following the observation of Goodwin (1952) on himself that 5 mg. of pyrimethamine daily could suppress malaria, Vincke (1952) carried out a successful mass prophylaxis in the Belgian Congo with a weekly dose of 25 mg. Covell *et al.* (1953) obtained complete suppression of overt attack with 25 mg. of pyrimethamine weekly in non-immune subjects exposed to a West African strain of *P. falciparum*.

Our observation in a village school indicates that weekly doses of 25 mg. have an effective suppressive action against malaria. Both falciparum and vivax infections have been prevalent in the area, the majority being falciparum. The persistence of *P. falciparum* parasites in a few cases during pyrimethamine administration indicates that some falciparum strains are relatively less sensitive to the drug. However, the large majority of the cases were free from parasites during the prophylactic regimen.

Our thanks are due to the Wellcome Foundation Ltd. for the supply of daraprim and to Sri C. L. Mitter, S. Mitter, and B. Dutta for their help in this work.

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Fatal Case of Agranulocytosis Due to "Novalgin"

The danger of agranulocytosis due to amidopyrine and its derivatives is now so well known that few would wittingly advise the use of these drugs, yet this may be done unintentionally by prescribing certain proprietary preparations. Frequently the proprietary name gives no indication of the precise nature of the active principle, and thus cases of agranulocytosis due to amidopyrine or closely related compounds continue to occur. It seems that the exclusion by law of amidopyrine from proprietary preparations, as is done in Denmark, is the only sure way of preventing these fatalities (*Lancet*, 1951). Meantime, publication of cases may result in a wider appreciation of this hidden danger and so help to minimize it.

CASE REPORT

A married woman aged 67 was admitted to the surgical wards of the Western Infirmary, Glasgow, on November 7, 1953, complaining of vomiting and the passage of red blood per rectum of a week's duration. She had been operated on for haemorrhoids on two occasions and had received injections of liver extract for anaemia over the previous three to four years.

On admission she did not look very ill and her temperature was 100.4° F. (38° C.). The throat was red and oedematous; proctoscopy revealed an indurated, elevated sinuous ulcer on the anterior wall of the rectum. After three days in hospital she was still febrile and appeared slightly jaundiced. The diagnosis of agranulocytosis was established by blood examination, which showed: Hb, 13.4 g. per 100 ml.; P.C.V., 43%; red cells, 4,720,000 per c.mm.; white cells, 75 per c.mm.; icteric index, 25 units. The blood film showed normal red cells and adequate platelets, but white blood cells were extremely scanty. Of the first 50 leucocytes examined 2 were polymorphs, 10 monocytes, 36 lymphocytes, and 2 Türk irritation cells.

Inquiry revealed that, to control headache, novalgin had been taken occasionally for years, but during the last month 15 gr. (3 tablets) were ingested daily in divided doses up to the time of admission. The only other medicaments taken during the previous three months were a vegetable laxative and liver extract; in particular, no barbiturate drug had been used.

Intensive treatment with penicillin brought considerable improvement and a reduction in temperature, but five days after admission she suddenly became distressed and dyspnoeic. Treatment for massive pulmonary embolism was at once instituted, but she died within two hours.

The significant post-mortem findings were as follows. Slight icterus; throat merely slightly injected. A coiled embolus 1 cm. in diameter lay across the bifurcation of the pulmonary artery. The embolus was massive and as much as 25 cm. could be removed in one piece; the right side of the heart was acutely dilated. On dissection of the leg veins both femorals were found to be clear, but the intramuscular tributaries on the right side contained thrombus; it was concluded that embolus had originated in the right femoral vein. On the anterior wall of the rectum there was an elevated irregular area of ulceration 4 by 2 cm. which extended into the anal canal. The necrotic tissue was greenish on the surface and dull yellow underneath. The necrosis extended into the bowel wall for 3 cm. and the adjacent tissues were severely inflamed and oedematous. The bone marrow was hyperplastic, red marrow extending half-way down the femur. The spleen weighed 250 g., and neither it nor any of the other blood-forming tissues showed evidence of leukaemia. The liver showed merely toxic cloudy swelling.

On microscopical examination the rectal ulcer showed the typical appearance of an agranulocytic lesion, the cellular infiltrate being composed almost entirely of mononuclears, and necrosis and inflammatory oedema being very severe and widespread. The marrow contained numerous foci of erythroblasts, and megakaryocytes were also plentiful; polymorphs were absent and myelocytes were scanty. The marrow thus showed a severe maturation arrest of granulopoiesis amounting to aplasia, but no evidence of either leukaemia or panmyelophthisis.

COMMENT

The post-mortem findings establish the cause of death as pulmonary embolism following right femoral thrombosis in a case of agranulocytosis. The neutropenia was clearly due to failure of granulopoiesis without there being any disease process in the marrow to account for it. Since there was nothing to suggest splenic neutropenia (Hutchison and Alexander, 1954), and no history of cyclic attacks, but a clear history of the habitual use of novalgin, a sulphonated compound of amidopyrine known to have caused agranulocytosis, it seems reasonable again to incriminate this drug. The findings in our case correspond closely with previous accounts of agranulocytosis due to novalgin (Benjamin and Biederman, 1936; Klumpp, 1937; Plum, 1937); in particular, the unusually low white-cell count which we observed has been met with in other novalgin cases (Fitz-Hugh and Comroe, 1933; Ridpath, 1934), and ulceration of the rectum is recorded in the case described by Buck (1929).

The introduction of antibiotics has altogether transformed the prognosis in cases of agranulocytosis by controlling the generalized infections which formerly proved rapidly fatal. It seems probable that had embolism not occurred this patient's life might not have been forfeit to novalgin, for under treatment with penicillin she was not profoundly ill and her blood culture was negative. It is, however, evident from examination of her marrow after death that several more days would have been required to see her out of the danger period due to agranulocytosis; the precursors of the polymorphs had not returned to the marrow, and so recovery was not yet in sight.

We are grateful to Professor C. F. W. Illingworth for permission to report this case.

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Thomas's Sign, or the Silver Stool in Cancer of the Ampulla of Vater

Dr. A. M. Thomas, pathologist to the Royal Masonic Hospital, has pointed out that in cancer involving the ampulla of Vater the patient sometimes passes "silver stools"—that is, motions having the colour of oxidized silver or aluminium paint. The silver or grey stool is a combination of the white stool of obstructive jaundice and the black stool of melaena.

Biliary obstruction, whatever its cause, will produce a clay-coloured stool. Such a stool may contain blood from many sources. If the amount of blood is small it will not colour the stool appreciably. If it is large it will dominate the picture and lead to the typical black stool of melaena, but massive intestinal haemorrhage is either intermittent or fatal. If the blood comes from low down it will be red and not black. The combination of deep jaundice with steady intestinal haemorrhage coming from high up in the intestinal tract is seen regularly in cancer of the ampulla, and only rarely in other conditions.

CASE 1

A married woman aged 46 was admitted on September 30, 1952, with a history of intermittent jaundice for three months. She did not appear to have lost weight, but was very anaemic. Tests showed the jaundice to be of the obstructive type, and the stools contained occult blood in large amounts. The barium meal was reported to be normal, apart from spasticity of the pyloric antrum.

A laparotomy was performed on October 16. A carcinoma could be felt at the ampulla. The gall-bladder and common bile duct were grossly distended, and both contained white bile only. Cholecystostomy was performed. The discharge from the drain soon became green in colour. On October 30 pancreatico-duodenectomy was performed with ligature of the stump of the pancreas and implantation of the bile duct in the jejunum. Apart from some blood-stained discharge, convalescence was satisfactory.

Since discharge on January 1, 1953, the patient has remained very well, needing only small doses of insulin. She dislikes fats, but that has benefited two people—her in that she has regained her youthful figure, and me in that she sends me a regular supply of Devonshire cream.

CASE 2

A man aged 78 was admitted on February 14, 1954, with a suprapubic fistula, following prostatectomy at another hospital in November, 1953. His haemoglobin level was 50% and his general condition poor. He was given two pints (1,130 ml.) of packed cells, and shortly afterwards developed jaundice which at the time was attributed to the transfusion. His stools were sent for analysis, and Dr. Thomas reported that they had the silvery appearance that he had previously noted in Case 1. On this appearance he made a tentative diagnosis of carcinoma of the ampulla of Vater.

The jaundice deepened and the patient died on February 22 in hepatic failure. At necropsy a carcinoma 3 mm. in diameter was found at the ampulla of Vater. The haemorrhage on which the diagnosis had been made had, however, come from a colonic diverticulum.

COMMENT

The diagnosis has since been made in two further cases. So far as I am aware the silver stool has never been described before. I bring the sign to the attention of surgeons because Dr. Thomas has not yet reported it himself and, being a pathologist, he is likely to report it in a journal read only by his brother pathologists. Thomas's sign, which can be observed by a house-surgeon or nurse who is aware of its importance, is diagnostic of cancer of the ampulla of Vater, and will enable instances of this eminently curable lesion to be recognized at an early and operable stage.

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Reviews

CEREBROVASCULAR DISEASE

Cerebrovascular Disease. By James Peter Murphy, M.D. Foreword by Percival Bailey, M.D. (Pp. 408; illustrated. 90s.) Chicago: The Year Book Publishers, Inc. London: Interscience Publishers Ltd. 1954.

This scholarly work includes a survey of the anatomy and pathology of cerebrovascular disorders. These are then related to the clinical syndromes of disturbance of cerebral blood supply. There are chapters which have great contemporary interest, notably that dealing with the vexed problem of spasm of cerebral arteries and that concerned with occlusion of the whole carotid artery itself. Although cerebral angiography has so greatly increased our understanding of the events leading to brain dysfunction through anaemia or haemorrhage, knowledge of the physiology of the cerebral circulation is still pathetically inadequate, so that we are still inclined to consider events as though they they were hydrostatic, in a field where hydrodynamic pressure gradients are all-important. The study of morbid anatomical specimens has encouraged the persistence of a static anatomical attitude to the problems, and so far the observation of flows through arteriography has done little to correct that attitude. Throughout Dr. Murphy's book there is apparent an awareness of this difficulty with an emphasis upon the activity of the vascular system as well as upon its structure.

Modification of intracerebral events by change in the vascular bed and in blood flow has been attempted in a number of contemporary procedures used in patients with hemiplegia of vascular origin. These have included, on the surgical side, stellate block, perfusion, and sympathectomy of the carotid vessels, and, on the medical, the immediate use of anticoagulants. Some recovery from vascular accidents being usual without intervention, it has been difficult to assess the results of these radical methods of management, but there is already a tendency to return to the more conservative methods of management which most neurologists have not forsaken. The subject remains, however, a controversial one. While the author has discussed the whole of this question in detail, he has done so in a balanced and thoughtful way which will give comfort to the conservative. At the same time, writing as a neurological surgeon, the author has included the appraisal, not obscured by details of technique, of the radical management of vascular anomalies of the convexity and of the basal vessels.

The work is a balanced one, whether dealing with the management of the lesion itself, of the symptoms to which it gives rise, or of the patient as a whole. Each chapter is followed by an adequate bibliography and is extensively illustrated by photographs of patients, specimens, radiographs, and experimental procedures. The volume contains an opportune review of the present knowledge of a subject whose literature extends to the beginnings of medicine.

DENIS WILLIAMS.

ABOUT WOMEN

Woman: Man's Equal? By Sir Adolphe Abrahams, O.B.E., M.D., F.R.C.P. (Pp. 176. 10s. 6d.) London: Christopher Johnson. 1954.

This may be regarded as a companion volume to the author's previous work, *Fitness for the Average Man*, the change in the title being made necessary by the fact that "nobody would be so foolhardy as to regard any woman as 'average.'" Whenever I read a book by Sir Adolphe Abrahams I am forcibly brought back to Laotse's "philosophy of the old rogue." Instead of reading a book about women by an eminent Western physician, I seem to be perusing the translation of an old Chinese manuscript written by, say, Chaung-tzu or, if not by that great master himself, at least by one of his disciples. So strong is this feeling that when I lay down *Woman: Man's Equal?* I see in imagination its distinguished author no longer dressed as usual, but suitably arrayed in Chinese robes.

Far from insulting Sir Adolphe by associating him with the philosophy of the old rogue, I am according him the highest praise, for this philosophy is the product of the highest wisdom. There is a benevolence, a charitableness, and a good-natured humour in the works of Chaung-tzu and also in this book which makes them exceedingly pleasant to read. The author has undoubtedly enjoyed writing *Woman: Man's Equal*, and now his enjoyment seems to come back out of its pages to meet us.

Sir Adolphe deals with a motley of subjects, some of which at first sight would appear to be only remotely related to women, but all combine together to form an excellent dish. Everybody will find something to enjoy in this book and something to condemn in it, for, like the subject with which it deals, it is full of paradoxes, absurdities, and contradictions. I commend it to "misogynists, philogynists, feminists, romanticists, idealists, cynics, knights errant, realists, and rhapsodists"—to everybody indeed except the humourless moron. For the sake of our reputations, therefore, it will be necessary for us all to buy it.

KENNETH WALKER.

CARDIAC CATHETERIZATION

Der Herzkatheterismus bei Angeborenen und Erworbenen Herzfehlern. By Professor Dr. Otto Bayer, Dr. Franz Wolter Loogen, and Dr. Hans Helmut. (Pp. 191+xii; 131 illustrations. D.M. 36.) Stuttgart: Georg Thieme. 1954.

In this book on cardiac catheterization in congenital and acquired heart lesions the authors give an account of this method of investigating heart disease based on 800 cases seen at Düsseldorf. Practically all the congenital lesions which exist to an age when investigation can be carried out are included. The first part of the book consists of a general description of materials and technique. There is a full account of Professor Bayer's method of calculating the areas of the pulmonary and mitral openings. The untoward results of the introduction of the catheter into the heart are described. There are well-written clinical and pathological introductions to each section, and these are usually clear and concise.

The schematic representations of the effects of lesions on the circulation need more explanation; they appear to be imitated without acknowledgment from Cournand's book, where they are much better done. The skiagrams are good. The cardiograms do not give the unipolar limb leads, and the other leads are not always labelled. Many of the recordings are marred by alternating current, and their description is often obscured with a curious use of the word "vector." The diagnosis of intra-auricular block needs some explanation. The pressure tracings are for the most part good, but some are poor and blurred and the whole curve is not always included. The phonocardiograms are also often blurred and indistinct. It is rather confusing to read first on one page that an atrial septal defect may cause a presystolic, on another a systolic, and on a third a diastolic murmur.

There is a list of references at the end of the book. This is not free from mistakes, and there is no link between it and the text.

TERENCE EAST.

OBSTETRICAL ESSAYS

Practical Obstetrics. By Bruce T. Mayes, M.V.O., M.B., B.S., F.R.C.S.(Edin.), F.R.A.C.S., F.R.C.O.G. Foreword by John A. Stallworthy, M.A., F.R.C.S., F.R.C.O.G. (Pp. 500; illustrated. 87s. 6d.) London and Sydney: Angus and Robertson. 1954.

This book first appeared in 1947, when it represented a collection of refresher "bulletins" prepared for medical officers serving in the Forces. It is now considerably modified and enlarged, and many will recognize it as a permanent

record of lectures delivered by Professor Bruce Mayes in this country while he was the Sims–Black Travelling Professor for 1954. The 38 chapters would be better termed "essays"—essays in the style of the older obstetricians who taught by detailed and graphic description of personally observed and treated cases, sometimes pointing out the moral themselves, often leaving and stimulating the reader to reach his own conclusion by approval or disagreement. They are suitable for reading in spare moments, for each is a separate entity. Most of the subjects fall within the range of obstetrics proper, but Professor Bruce Mayes does not hesitate to wander into the bypaths of dysmenorrhoea, sterility, and consulting-room technique. To one and all, however, he brings charm, wit, neat phrase, happy aphorism, and a philosophy based on clinical experience.

The book is an exposition of the art rather than the science of modern obstetrics, and it savours of the fireside chats of a wise doctor to general-practitioner obstetricians working in conditions in which they may have to take a good deal of clinical responsibility without having expert help immediately at hand. Scientific data and explanation are not allowed to take precedence over common sense; indeed, they are sometimes omitted, invented, or slightly distorted in order to provide a simple and logical working basis. But surely this falls within the bounds of teaching licence, and it is one of the secrets of the author's exceptional gifts as a teacher. Another is an appreciation of the psychological reactions of students and readers. On page 1 of Chapter I there is a footnote: "If you are in a hurry I suggest moving on to Chapter IV." This is enough to make even a reviewer hesitate to skip Chapters, I, II, and III.

T. N. A. JEFFCOATE.

CANCER

Cancer: Diagnosis, Treatment and Prognosis. By Lauren V. Ackerman, M.D., and Juan A. del Regato, M.D. Second edition. (Pp. 1,201; 702 illustrations, 23 colour reproductions. £8 10s.) London: Henry Kimpton. 1954.

This is a very unusual book containing an immense amount of valuable information and obviously based on wide experience and an extensive study of the literature, to which there are copious references. But its character can be appreciated only when it is realized that it is the work of a pathologist and a radiologist, both of great eminence in their respective fields. Their approach is therefore quite different from that of the surgeon, with his outlook primarily clinical and technical. This is perhaps best seen in the discussion of cancer of the respiratory tract, fully illustrated by diagrams and pathological photographs. But the interest is in large groups of cases and not in the treatment of any individual case.

The volume is chiefly of value for the careful and accurate description which it gives of the origin and spread of cancer in different regions, for its discussion of the relative value of surgery and radiotherapy, and for the full bibliography which it presents. It is admirably illustrated by diagrams, photographs, and photomicrographs.

HENRY SOUTTAR.

PSYCHOTIC ART

Insanity, Art, and Culture. By Francis Reitman, M.D., D.P.M. (Pp. 111; illustrated. 12s. 6d.) Bristol: John Wright and Sons, Ltd. 1954

Psychotic patients have made drawings and paintings from time immemorial. These were not taken seriously until the latter part of the nineteenth century, when Simon and Lombroso used the productions for diagnostic purposes. The present-day revival of interest in imaginative art is focused mainly upon its use as a therapeutic agent; the diagnostic hints conveyed in the pictures are not missed, and now and then may be used to supplement other knowledge.

Dr. Reitman considers only the diagnostic significance of psychotic paintings. This narrow topic is amplified by some reflections on the symptomatic significance of the art products of psychotics in other countries. To this end material was collected from mental hospitals in Asia, Africa, North America, and New Zealand. The aim of this comparative study is obscure, and certainly the results are not decisive, as might have been anticipated from the small number of pictures available. The author himself appears to attach little importance to the few conclusions reached.

Commenting on symbols, the author recalls the familiar fact that Freud and Jung (and their pupils) attach different values to the word "symbol." Freud's view is not given, but Jung is misrepresented as holding that symbols express "mystic collective images." Having brushed Freud and Jung aside, Dr. Reitman tells us what symbols are "in scientific usage"; they are "objects which are attended to not for their own sake, but for the sake of something else to which they refer." By this token the ringing of the telephone bell would be a symbol. But happily "scientific usage" as here understood is not the language of artists, psychotic or otherwise.

E. A. BENNET.

ELECTRONICS FOR PHYSIOLOGISTS

An Introduction to Electronics for Physiological Workers. By I. C. Whitfield, B.Sc., Ph.D. (Pp. 236; illustrated. 18s.) London: Macmillan and Co., Ltd. 1953.

It is very difficult to-day for a physiologist to avoid the use of electronic apparatus such as amplifiers, cathode-ray oscillographs, and electronic stimulators, which have become essential pieces of equipment in almost every branch of physiological research. While expert advice can always be obtained on problems of electronics, it is obviously better for the physiologist himself to have some understanding of his apparatus and methods, however complex or specialized they may be.

This book sets out to fill a gap between the elementary radio textbook and the more specialized monograph dealing with electronics and biological research. In the earlier chapters the author gives an account of the fundamental ideas of electronics, with due emphasis on those parts of the subject which have special importance in biological work. A certain background of electrical theory and elementary physics is assumed, and these chapters serve rather as a reminder of earlier and possibly forgotten groundwork. The chapters dealing with amplifiers and oscillators are more detailed, and quantitative treatment has been given when possible, thus giving the book an essentially practical slant. The problems of "noise," interference, and screening have been clearly and simply dealt with, and the author discusses in some detail the important question of electrode and inter-electrode resistance. Throughout the book there are references for further reading; as the author points out in his foreword, this book is not for those who hope, in an idle hour, to pick up something about electronics.

W. F. FLOYD.

When Rush Medical College was opened in Chicago in 1843 about thirty other medical schools were already functioning in the U.S.A., many of them patterned after the Edinburgh school. Benjamin Rush, after whom the college was named, was an Edinburgh graduate, a friend of Benjamin Franklin, a signatory of the Declaration of Independence, and the first great American physician. He introduced clinical teaching at Pennsylvania Hospital, to which he was physician for 30 years. He died in 1813. Rush Medical College was founded by Daniel Brainard. In its first year the requirements for the M.D. degree were three years of study with a respectable physician, two courses of lectures (the second at the school) and the submission of a thesis. In 1877 the college decided to establish a hospital, which opened in 1883 as the Presbyterian Hospital. After affiliation with the University of Chicago in 1898, Rush became an integral part of the University in 1923, but as time passed the plan to confine the college to postgraduate education became less appealing to Rush and to the hospital, and the union was dissolved in 1941, leaving Rush once again independent. Its history is briefly told by Ernest E. Irons in *The Story of Rush Medical College* (Chicago, published by the College, 1953), a book of 82 pages which is a useful addition to the history of medical education in the U.S.A.

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INFLUENZA

Our old winter enemy influenza is with us once again, though if it is any consolation to either patient or doctor it appears that virus B, which is usually associated with a less severe form of illness, has been mainly responsible so far. But it is too early to predict the future course of events. In its true epidemic form influenza presents a characteristic picture familiar to all, but there are many occasions when diagnosis on purely clinical grounds is not so simple. Influenza is not notifiable in the United Kingdom, but the certified deaths from influenza and pneumonia in the 160 great towns (formerly 126) of England and Wales indicate the general trend of acute respiratory infection. Clearly this is a very crude index of influenza, and the recent introduction of a "spotting scheme" in which selected general practitioners and regional laboratories have co-operated has already made progress in determining the part played by the influenza viruses in respiratory disease.[1] At an international level the World Influenza Centre is concerned with the serological classification of virus strains[2] and in tracing the spread of the disease.[3]

Two main serological types of influenza virus, A and B, are now recognized. A third, C, has been described, but its role in human disease is not yet understood. It appears to be associated with a minor form of illness.[4] All major epidemics, which occur on an average every two to three years,[5] have been associated with virus A. Virus B, on the other hand, tends to be endemic and an annual source of mild influenza,[5] but epidemics have been caused by it.[6] Recently virus A has been responsible for extensive and, in some areas, severe influenza—during the winters of 1950–1 and 1952–3. Virtually no influenza was encountered in 1951–2 and 1953–4.

In the past twelve months sporadic cases due to virus A occurred in February, 1954, and a few cases of influenza B in the spring, with a sharp outbreak at a school in the midlands. During the summer virus A was detected in cases arriving by sea from South Africa, but the disease did not spread in Britain. In September influenza appeared in Wales, later on Tyneside. Within the next few weeks many cases were reported in Scotland and in general north of a line joining the Humber and the Severn. Serological evidence of virus B was obtained. By the end of the year similar cases appeared in the south and in the London area. Occasional cases of virus A and of virus C have also been encountered. People of all ages have been affected, but several reports have indicated a high attack rate in school-children. The weekly figures of certified deaths from influenza up to January 8 have been 56, 66, 56, 82, and 102; the deaths seem to be chiefly of elderly people. These figures show a fairly sharp rise and it is too early to say how the outbreak will compare with those of previous years. The general impression so far is one of increased prevalence, with local outbreaks, and is not unlike the behaviour of influenza B in 1945–6.[9] On the whole the behaviour of virus B this winter is in keeping with the idea that influenza due to this virus is generally less severe than that caused by virus A, but it is impossible to distinguish the two on clinical grounds alone.

In addition to true virus influenza a number of less well differentiated respiratory infections have been reported. Influenza-like illnesses (but without influenza virus) have occurred all over the country; so-called influenza with vomiting (distinct from epidemic nausea and vomiting) and other cases with encephalitic symptoms have been seen. An increased incidence of virus or primary atypical pneumonia has also been reported. There is certainly plenty of scope for sorting out this mixed collection of acute respiratory infections into aetiological types.

Prophylactic immunization with killed virus vaccines prepared in the fertile egg has given encouraging results; the timing of the vaccination and the incorporation of the correct virus strains are important.[7,8] The main disadvantages are the short-term effect of such vaccines—research into this is now in progress—and also the cost. Vaccination is likely to be practicable only in protecting selected groups of individuals rather than the population as a whole. No drug has yet been found effective against influenza or indeed against any of the small viruses. Many have been tried.[9] Prophylactic chemotherapy to control secondary bacterial infection in uncomplicated influenza is best reserved for those patients with existing lung disease or for old or debilitated patients; on the other hand, influenza complicated by bronchiolitis or pneumonia requires energetic

[1] *Monthly Bull. Minist. Hlth (Lond.)*, 1954, 206.
[2] Andrewes, C. H., *Wld Hlth Org. Monograph Series*, 1954, No. 20, 9.
[3] Isaacs, A., and Archetti, I., *Lancet*, 1954, **2**, 457.
[4] Francis, T., *et al.*, *Science*, 1950, **112**, 495.
[5] Isaacs, A., *Brit. med. Bull.*, 1953, **9**, 208.
[6] Dudgeon, J. A., *et al.*, *Lancet*, 1946, **2**, 627.
[7] Report by M.R.C. Committee, *British Medical Journal*, 1953, **2**, 1173.
[8] Francis, T., *Wld Hlth Org. Monograph Series*, 1954, No. 20, 125.
[9] Hurst, E. Weston, *Brit. med. Bull.*, 1953, **9**, 180.
[10] Stuart-Harris, C. H., *Influenza*, 1953.
[11] Mulder, J., and Stuart-Harris, C. H., *Wld Hlth Org. Monograph Series*, 1954, No. 20, 141.

treatment with antibiotics.[10 11] Until such time as a specific anti-viral compound is produced the best advice is to stay in bed and keep warm.

POST-OPERATIVE WEIGHT LOSS

It is not clear whether the phase of weight loss and protein catabolism which follows fractures[1 2] and surgical operations[3–6] is part of the defence of the body against trauma, as Moore believes,[7] or whether it is due solely to the restriction of caloric intake in the immediate post-operative period, as the experiments of Werner suggest.[8] What is certain is that convalescence is prolonged and wound healing delayed in patients coming to operation in a poorly nourished state. One surgeon shares Julius Caesar's preference for the fat, who he finds stand major surgery better than thin people, presumably because they have a large store of potential calories on which to draw after the operation.[9] Poorly nourished patients have been shown to have a "predepleted metabolic response" to operation, which consists in only small negative nitrogen and potassium balances, with a potassium/nitrogen ratio approximating to that found in the tissues.[10] The protein and caloric reserve of such patients should be built up before operation, and even the frailest patient may gain weight and strength to withstand major surgery by a regime of forced feeding with a high-protein and high-caloric intake.[9] Patients who are assessed as being well nourished before operation can, by forced feeding, retain enough nitrogen in the pre-operative period to allow for their post-operative loss and still leave them in positive balance over the whole period before, during, and after operation.[11]

In the post-operative period some investigators have found it impossible to meet the demands of the body for nitrogen to replace what is lost in the catabolic phase.[6 12] In this issue of the *Journal* Drs. D. Davies and A. Pines report (p. 200) that they were unable to arrest post-operative weight loss in tuberculous patients, who were taking an ordinary hospital diet, by the administration of the protein anabolic hormone methylandrostenediol. Details are not given of the amount of calories and nitrogen their patients were receiving, and it is possible that the dietary intake may have been surprisingly low, especially in calories. Sutherland has suggested a number of reasons for this from her experience in Edinburgh, which she believes may be applicable in hospitals elsewhere.[13] On the other hand, Riegel *et al.*[14] were able to maintain their patients in nitrogen balance or positive nitrogen balance during the first five days after operation with an intake which supplied 0.3 g. nitrogen and 30 calories per kg. body weight per day. This is modest compared with the amounts Brain regards as necessary for his malnourished patients during the pre-operative period.[9] Although in short-term experiments it is possible to maintain nitrogen balance with an adequate nitrogen intake and without additional calories,[15] those who have been wholly or partly successful in anticipating[11] or covering the loss of weight and nitrogen after operation all stress the importance of adequate caloric intake,[14 16] particularly for patients with burns.[18]

When possible, food should be given by mouth. Patients unable to take it thus in the pre-operative period may receive it through a preliminary gastrostomy or jejunostomy, though care must be taken when feeding by jejunostomy not to give hypertonic feeds, which the jejunum does not tolerate well.[14] Some patients regain their appetite as their nutritional state improves on this regime.[9] Even when there is no obstacle to oral feeding, loss of appetite may make it impossible to provide an adequate caloric intake, and in such cases tube-feeding may be necessary. This is often successful if the patient can tolerate it, but may be complicated by severe dehydration.[17] The amount absorbed, even of glucose and water, is too uncertain to make rectal feeding with amino-acid mixtures a desirable method.[16]

When some form of alimentary feeding is not possible food must be injected intravenously. Whole protein in the form of blood transfusions, plasma infusions, and human serum albumin have been successfully administered,[16] or perhaps more commonly protein hydrolysates. A. W. Wilkinson *et al.*[6] found that the use of such preparations merely increased the urinary nitrogen excretion to an amount nearly equivalent to the amount given as the hydrolysate. Whatever the method for giving the nitrogen intravenously, it is in the provision of calories that the difficulties arise. If glucose alone is added to the source of nitrogen for this purpose, extremely hypertonic solutions must be used, which cause thrombosis in peripheral veins, though they may be infused slowly

[1] Cuthbertson, D. P., *Biochem. J.*, 1930, **24**, 1244.
[2] —— ibid., 1931, **25**, 236.
[3] Howard, J. E., *et al.*, *Bull. Johns Hopk. Hosp.*, 1944, **75**, 156.
[4] Brunschwig, A., *et al.*, *Ann. Surg.*, 1942, **115**, 1091.
[5] Riegel, C., *et al.*, *J. clin. Invest.*, 1947, **26**, 18.
[6] Wilkinson, A. W., *et al.*, *Lancet*, 1950, **1**, 533.
[7] Moore, F. D., *Nutr. Abstr. Rev.*, 1948, **6**, 161.
[8] Weiner, S. C., *et al.*, *Ann. Surg.*, 1949, **130**, 688.
[9] Brain, R. A. I. F., *Proc. roy. Soc. Med.*, 1954, **47**, 987.
[10] Moore, F. D., and Ball, M. R., *The Metabolic Response to Surgery*, 1952. Springfield, Illinois.
[11] Koop, C. E., *et al.*, *Ann. Surg.*, 1946, **124**, 1165.
[12] Cuthbertson, D. P., *Brit. J. Surg.*, 1936, **23**, 505.
[13] Sutherland, A. B., *Proc. roy. Soc. Med.*, 1954, **47**, 995.
[14] Riegel, C., *et al.*, *J. clin. Invest.*, 1947, **26**, 18.
[15] Elman, R., *Parenteral Nutrition*, 1947, New York.
[16] Rhoads, J. E., *Fed. Proc.*, 1952, **11**, 659.
[17] Engel, F. L., and Jaeger, C., *Amer. J. Med.*, 1954, **17**, 196.
[18] Russell, C. S., *et al.*, *Lancet*, 1954, **1**, 902.
[19] Moore, D. C., and Kowp, M., *Surg. Gynec. Obstet.*, 1945, **80**, 523.
[20] Rice, C. O., *et al.*, *Ann. Surg.*, 1950, **131**, 289.
[21] Shafiroff, B. P., *et al.*, *Surg. Gynec. Obstet.*, 1949, **89**, 398.
[22] —— and Mulholland, J. H., *Ann. Surg.*, 1951, **133**, 145.
[23] Van Itallie, T. B., *et al.*, *Arch. intern. Med.*, 1952, **89**, 353.
[24] Kinsell, L. W., *et al.*, *Calif. Med.*, 1954, **81**, 218.

with safety into the inferior vena cava.[18] Alcohol, which has a high caloric value, has been given intravenously in mixtures with amino-acids and glucose.[19 20] It is said to have the additional advantage of raising morale and reducing the need for morphine, and to be non-toxic in the quantities employed.[20] But the material of choice for the caloric component of intravenous feeding is fat. Fat emulsions have a high caloric value and high molecular weight, with a low osmotic pressure, so that they can be used in only slightly hypertonic concentrations. There is considerable evidence of their value as an intravenous source of calories,[21–24] but unfortunately they are not generally available in Britain.

FUNGUS ALLERGENS

The dense fog that suddenly enveloped part of London last Sunday was a sharp reminder again that city smoke is a menace to health. Now another aspect of air pollution has been reviewed by Kate Maunsell.[1] She has pointed out the many problems that arise from sensitization due to inhalation of fungal spores. The potential sensitizing effect of grass pollen and *Penicillium* spores was first noted by C. H. Blackley,[2] of Manchester, over a hundred years ago. His observations were largely forgotten, as were his classical experiments when he demonstrated by means of pollen traps and skin tests that grass pollen was the cause of summer catarrh. After sixty years W. S. Van Leeuwen,[3] in Holland, became interested in the moulds as a cause of respiratory allergy, and by 1946 H. A. Hyde and D. A. Williams,[4] at Cardiff, had begun their systematic study on the pollen and spore content of the air. The usual method of tracing the common airborne fungi was by exposing Petri dishes containing suitable culture media, though many fungi for various reasons will not grow on the ordinary laboratory media. More recently quantitative techniques have been used. A measured sample of air impinges on a sticky glass slide, and in the automatic spore trap devised by J. M. Hirst[5] the trapped particles can be graded in size. The number and different types of fungal spores as well as other potential sensitizers and bronchial irritants can be measured hourly or daily, and the seasonal variations can be studied.

M. Richards,[6] when working for the Asthma Research Council, made a survey of the spore content of the air at nine different stations in Great Britain. He found that, as well as a seasonal variation, there is a considerable difference in mould spore content between town and country. The increase in spores occurs from April to November, rising to a high peak in July and August. In patients allergic to fungus spores symptoms of hay fever, sometimes with an associated asthma, occur during the months of the heaviest spore cloud. The symptoms may be combined with other inhalant allergies, particularly to grass pollen. A knowledge of both the pollen and mould spore seasons is therefore necessary before investigating patients with seasonal symptoms. Symptoms during June to mid-July are almost certainly, if confined to this period, caused by grass pollen. Symptoms from mid-July to September are probably due to fungal spores, and generally to those of *Cladosporium*. In a pollen-sensitive patient eye irritation is nearly always one of the symptoms, while a patient sensitive to mould spores does not seem to experience this. The antigenic extracts made from mould spores are much weaker than pollen extracts. Intradermal testing with pollen extracts, except with very diluted solutions, is not recommended owing to the likelihood, except in experienced hands, of a severe constitutional reaction in a sensitive patient, while intradermal testing is the method of choice in a mould-sensitive allergic patient. In general the treatment of the mould-sensitive patient is much the same as the pollen-sensitive—a careful history, confirmatory skin tests, and hyposensitization when dust elimination or symptomatic drugs do not afford relief.

Fungi are more prevalent in humid areas, and many patients report aggravation of symptoms near rivers and in valleys, especially on clay soil. The east and south-east coasts of England suit the mould-sensitive patient, but not the coastal areas of Dorset, Devon, and Cornwall. Yet it is unwise to be dogmatic about suitability of localities, because there are marked local differences. Houses that have been slightly damaged by bombs, old houses, and houses that have had a blocked rain-water pipe may have become affected by the wood-destroying fungus of dry rot (*Merulius lacrymans*). A. W. Frankland and M. J. Hay[7] were the first to show that dry rot, which is so often quite unsuspected in a house, can give rise to inhalant allergic symptoms. Professor P. H. Gregory and his colleagues[8] found 75,000 spores per cubic metre of air in a cellar which contained dry rot, with 16,000 spores per cubic metre in the first-floor room. The occupational hazards of sensitization by mould spores are seen in dock workers unloading infected materials, particularly grain, second-hand furniture dealers, and gardeners, especially those growing tomato plants that become infected with *Cladosporium*. But perhaps it

[1] *J. Laryng.*, 1954, **68**, 765.
[2] *Catarrhus Aestivus* (*Hay fever*). 1873. London.
[3] *Proc. roy. Soc. Med.*, 1924, **17** (Therap. and Pharm. Sect.), 19.
[4] *Trans. Brit. mycol. Soc.*, 1946, **29**, 78.
[5] *Ann. appl. Biol.*, 1952, **39**, 257.
[6] *Int. Arch. Allergy*, 1953, **4**, 360.
[7] *Acta allerg.* (*Kbh.*), 1951, **4**, 186.
[8] Ibid., 1953, **6**, 168.
[9] Swaebly, M. A., and Christensen, C. M., *J. Allergy*, 1952, **23**, 370.

is the housewife who is most exposed, since it has been found[9] that up to 1,000,000 spores of the common fungi are present per gramme of household dust.

BACTERIAL GENETICS

The field of bacterial genetics is one in which discoveries of the highest importance, both to medicine and to genetics, have been made in recent years. Interest in the genetics of bacteria was aroused by two events: the finding by O. T. Avery, C. M. MacLeod, and M. McCarty[1] in 1944 that the capsular transforming agent in the pneumococcus was composed of deoxyribonucleic acid (D.N.A.), and the discovery by J. Lederberg and E. L. Tatum[2] in 1946 that interchange of hereditary material had occurred in the daughter-cells from a mixed culture of different strains of *Escherichia* (*Bacterium*) *coli*.

The report in this *Journal* last week[3] of the recent meeting on bacterial genetics held at the London School of Hygiene and Tropical Medicine reveals the remarkable advances made during the last decade. The hereditary mechanism of bacteria has been found to bear many resemblances to that of higher forms of life; notably in the occurrence of a particulate (as distinct from a blending) type of inheritance, associated with mutation, dominance, linkage, crossing-over, and linear linkage groups. On the other hand, bacteria show two major differences from normal Mendelian inheritance: first, in the elimination of a segment of the hereditary material from diploid cells, such as apparently occurs regularly in *E.* (*B.*) *coli*; and, secondly, in having mechanisms for the transfer of genetic material other than by close association of parent cells. These mechanisms include the phenomena of transformation—known in the pneumococcus, in *Haemophilus influenzae*, and in the meningococcus—in which the hereditary character of cells is permanently changed by treatment with D.N.A. obtained from another strain of the same species; and of transduction—known in *Salmonella*—where hereditary factors are transferred from one strain to another by means of bacteriophage. The hereditary mechanism of viruses, and in particular of bacteriophage, is closely bound up with that of the host. There is increasing evidence that the hereditary material of both bacteria and phage is composed of D.N.A. Indeed, phages behave in some respects as though they were part of a bacterium's genetic material which has come adrift from its proper place and has multiplied at the expense of the host.

There is still much to be learned about the mechanism of inheritance in bacteria. The realization that recombination of characters is apt to occur whenever a host is infected simultaneously by more than one strain of a pathogenic bacterium is of special significance in medicine. It implies that new strains of such bacteria, differing in biochemical and antigenic properties and in virulence, are apt to arise with much greater frequency than would be possible if these bacteria were merely propagated vegetatively. For the geneticist, the opportunity provided by bacteria and viruses for studying the properties of D.N.A. is of great value in elucidating the basis of inheritance, not merely in these organisms, but also in plants and animals generally, since D.N.A. appears to be the fabric of the gene. As mentioned in last week's report,[3] the separation by chromatography of D.N.A. obtained from streptomycin-resistant pneumococci into a number of fractions differing both in chemical composition and in transforming ability opens the possibility of establishing the chemical composition of a specific gene. Moreover, if a mutation such as from streptomycin-sensitivity to streptomycin-resistance comes to be understood chemically, then the control of such mutations will be a real possibility.

HISTONES AND CANCER

The nucleic acids, and especially deoxyribose nucleic acid (D.N.A.), the characteristic nucleic acid of the cell nucleus, have attracted much experimental work because of the suspicion that they carry the genetic characteristics of the cells (see preceding annotation). It is natural that some interest should be shown in the basic proteins which accompany the D.N.A. in the chromosomes. Little is known of the nature of these compounds, except perhaps the simple protamines, which occur in a limited group of fish sperm nuclei and have been extensively investigated by Felix at Frankfort.

The rather more complex basic proteins, known as histones, which occur in the nuclei of mammalian cells have been investigated by E. Stedman and E. Stedman.[4] In a recent communication H. J. Cruft, C. M. Mauritzen, and E. Stedman[5] present further evidence of the physico-chemical characterization of these substances, and claim, first, that the histones are cell-specific, and, secondly, that there is a qualitative difference between the histones of cancerous and those of normal cells. The last claim, if confirmed, would be of great importance. If the first proposition is true, the second necessarily follows. However, it would not be easy to prove this, since it would be necessary first to characterize the histones of all the normal cells of the organism. Unfortunately the characterization of the histones of even the most studied tissues, such as beef thymus, leaves a lot to be desired, and it is doubtful if the present information does much more than support a suspicion of differences between the histones of different tissues of one animal.

Even the number of histones present in normal tissues is doubtful. Cruft *et al.* regard a triple electrophoretic pattern as normal, consisting of a large central peak, which they attribute to the main histone, with subsidiary peaks on each side. J. A. V. Butler and his colleagues, however, have reported in a recent paper[6] that a histone solution which originally showed two electrophoretic

[1] Avery, O. T., *et al.*, *J. exp. Med.*, 1944, **79**, 137.
[2] Lederberg, J., and Tatum, E. L., *Cold Spr. Harb. Symp. quant. Biol.*, 1946, **11**, 113.
[3] *British Medical Journal*, 1955, **1**, 161.
[4] Stedman, E., and Stedman, E., *Philos. Trans. B*, 1951, **235**, 565.
[5] Cruft, H. J., Mauritzen, C. M., and Stedman, E., *Nature* (*Lond.*), 1954, **174**, 580.
[6] Davison, P. F., James, D. W. F., Shooter, K. V., and Butler, J. A. V., *Biochim. biophys. Acta*, 1954, **15**, 415.
[7] Butler, J. A. V., Davison, P. F., James, D. W. F., and Shooter, K. V., ibid., 1954, **13**, 224.

peaks gradually developed, on standing, a third intermediate peak, owing apparently to the formation of a complex of the two original components. The evidence given by Cruft *et al.* of the specificity of histone fractions derived from different tissues is also not very convincing to those who have had experience of establishing iso-electric points. The other test proposed is the occurrence of a single electrophoretic peak when histones from different tissues are dialysed together for sixty hours but a double peak when dialysed separately and mixed just before the electrophoresis is begun, but this hardly carries sufficient conviction in view of the changes which occur on prolonged dialysis in a neutral medium.[7] The proteins isolated by Cruft *et al.* from cancerous tissue (for example, an iso-electric point at about *p*H 7.0 is cited in one instance) are certainly so different from normal histones that a doubt remains whether they should be regarded as histones at all. An analysis of them would be of great interest. The conclusions reached by Croft, Mauritzen, and Stedman may well prove to be correct, but more research is needed before a critical estimate of the position can be made. An established claim to have discovered characteristic differences between normal and malignant cells would be a most notable advance, and the matter will no doubt be pursued further.

FLUORIDE IN WATER

Although some 1,000 communities in the United States have added fluoride to their water supply, the Select Committee of the House of Representatives was rightly cautious about the effects of this measure and suggested that in areas with a high fluoride level in the drinking water investigations should be made into bone development and diseases and kidney diseases. The Institute of Dental Research of the National Institute of Health and the Public Health Service undertook the study, and a team of workers has now completed a comprehensive survey in Texas.[1] The epidemiological experience of Bartlett, with the very high fluoride content of 8 p.p.m. in the water supply, was compared with that of Cameron, where the level was only 0.4 p.p.m. Both towns were similar in geographical situation and racial composition and they were mainly agricultural communities. The composition of the drinking water differed in other respects, that of Bartlett containing four times the amount of dissolved solids as that of Cameron. The largest differences between the components were in sodium and potassium, which together were 26 times greater in Bartlett than in Cameron, and chloride, which was 11 times greater.

The investigation was begun in 1943 and included only people who had been residents in the towns for the preceding fifteen years. The medical history since birth was recorded at the start of the study and the medical experience during the period 1943–53 was carefully reviewed. The number of persons concerned was 116 in Bartlett and 121 in Cameron. In both areas the males formed only one-third of the total. The age distribution of the population differed between the towns; 44.8 of the persons were over age 50 in Bartlett in 1943 compared with 24.8 in Cameron. Deaths were naturally more numerous during the ten years in Bartlett than in Cameron, there being 14 in Bartlett to 4 in Cameron. The difference between the age-corrected death rates was not statistically significant. The incidence of abnormal clinical findings was very similar in both towns. The only abnormality which had a significantly different incidence was disease of the cardiovascular system (except uncomplicated hypertension) with a percentage of 23.9% in Cameron and 12.5% in Bartlett. Bone changes were determined from radiographs taken in 1943 and 1953. The percentage abnormalities for changes in density, coarse trabeculation, hypertrophy, spurs, and osteoporosis were measured, but none of the differences were statistically significant. The only abnormal laboratory finding which was significant in both years was the differential count of neutrophils, the value in Bartlett being 21.1% in 1943 and 29.5% in 1953 compared with 8.5% and 15.9% in Cameron. Abnormalities in the white blood count were significantly larger in Bartlett in 1943—14.7% compared with 4.1% in Cameron—but not significantly larger in 1953—14.1% compared with 8.5%. The abnormality of albuminuria was significantly commoner in Cameron in 1943, being 8.3% compared with 2.6% in Bartlett; in 1953 the respective percentages were 14.1 and 6.5, and the difference was not significant. The authors conclude that apart from dental fluorosis in Bartlett and a higher rate of cardiovascular abnormalities in Cameron there were no significant differences between the findings in the two towns.

[1] *Publ. Hlth Rep.* (*Wash.*), 1954, **69**, 925.

VOLUNTEERS

Two features of the experimental situation need watching when volunteers are used as subjects for medical research: first, if inferences about average healthy subjects are to be drawn from the experiments, the subjects taking part in them ought preferably to be in that category; secondly, for ethical reasons the experimenter would wish to take only those subjects whose volunteering is entirely free of any unhealthy compulsion. A small investigation recently conducted into the psychology of a group of volunteers at the Harvard Medical School is a pertinent indicator that they may be a stranger lot than they seem at first sight. Some pharmacological experiments with drugs were being carried out on 56 supposedly healthy young men, nearly all college students, aged 21 to 28. The results of Rorschach tests on them and psychological interviews are reported by Lasagna and von Felsinger.[1] Among these 56 volunteers were found 3 with psychosis (2 of them practising homosexuality), 12 with psychoneurosis (1 under treatment and 6 seeking it), 3 with psychopathic personality, 1 alcoholic, 4 practising homosexuals (in addition to the 2 psychotics), 1 with severe peptic ulcer, and 1 with severe stutter. An investigation into the reasons for volunteering (apparently not confined to the maladjusted members

[1] *Science*, 1954, **120**, 359.
[2] *J. soc. Psychol.*, 1942, **16**, 259.
[3] *J. abnorm. soc. Psychol.*, 1952, **47**, 259.

of the group) showed that some took part for the monetary rewards, which are unspecified here. Some hoped to find professional help or "a drug that might prove 'the golden key' to their personality problems." Some were in search of new experiences; some sought release from personal problems. As might be expected, the subjective effects reported by some of these men when they were tested with various drugs such as pentobarbitone or mescaline bore a sufficiently strong relationship to the subject's personality to make generalization in a wider population hazardous.

Studying the volunteer response as such, Marlow found[2] in the course of an investigation into women's sexual behaviour that volunteering was associated with high dominance feeling and unconventional sexual conduct. Marlow and Sakoda,[3] studying some of Kinsey's subjects, report that volunteer groups consistently have a higher self-esteem score than non-volunteer groups. They recommend that when volunteers are used a test for volunteer error should be made before results of the tests are published as representative of a general population. This may be seen as the corollary of a normal practice in experimental laboratories—namely, the testing and standardization of materials with which experiments are carried out—and the Harvard investigation is a useful reminder of old principles in a rather unexpected context.

TREATMENT OF ASTHMA WITH CORTISONE AND A.C.T.H.

Although spectacular results have been obtained with cortisone and corticotrophin in the treatment of severe chronic asthma, there are four important reasons for caution. The treatment is not without danger; most patients who respond satisfactorily relapse when it is discontinued, and it is wise to presume that when cortisone therapy of chronic asthma is begun it may have to be continued indefinitely; many patients gain weight so quickly that adequate dosage cannot be maintained; and some fail to respond in any way. The rising number of fatalities is disturbing. Savidge and Brockbank[4] recently collected from published reports the details of eleven patients with severe bronchial asthma who had died under treatment: seven were having cortisone, two corticotrophin, and two both drugs. Until more is known of the mode of action of these substances they cannot be exonerated from blame. Furthermore, fatal anaphylactic reactions have been attributed to corticotrophin. The frequency with which patients relapse after treatment is well shown by recent statistics published by Kania and Schmidt,[5] who treated 111 patients with cortisone. Eighty-five were completely relieved, 21 were much improved, and 5 were not benefited. Relief was only temporary, and symptoms usually returned two to four weeks after cortisone was withdrawn. Unpleasant and even severe side-effects are often a consequence of long-continued treatment. The most common is the tendency to gain weight. Usually this is due to an increase in body fat, but sometimes a rapidly developing oedema is a result of the salt-conserving action of cortisone on the renal tubules. Experimentally these drugs have caused suprarenal atrophy and decalcification of bone. In spite of these serious disadvantages the use of cortisone and corticotrophin is fully justified if they can return health and happiness to severe chronic asthmatics who have resisted all other forms of treatment. Cortisone can achieve this.[6] Corticotrophin has been more difficult to obtain in this country, but has given excellent immediate results, notably in the relief of status asthmaticus. It has the disadvantage compared with cortisone that it must be given by injection, but the longer-acting A.C.T.H. gel seems equally effective and need be given only once daily. Elsewhere in this issue Dr. J. E. G. Pearson describes the successful treatment of 8 out of 10 patients with severe status asthmaticus or prolonged and incapacitating asthma, though his series also illustrates the tendency to relapse after treatment has ceased. This was not a blind trial of the remedy, though so far as was possible the patients were prevented from knowing that they were being given A.C.T.H.

The Medical Research Council is at present conducting a trial of the use of cortisone in the treatment of chronic asthma and status asthmaticus at a number of different centres. Trials of this kind must be strictly controlled, and so far as the doctors and patients are concerned must be blind trials. No one close to the patient must know whether cortisone or an inert substance is being used, because the knowledge that a new form of treatment is being tried is likely to have a strong psychological influence on the asthmatic patient. Some patients have done astonishingly well for many months on inert preparations; and some are loud in their praise of the benefits of cortisone, although they have never had any except in their imagination. All physicians who have had experience with these drugs emphasize that it is wise to restrict them to cases of chronic asthma in which every other treatment has been tried and failed and to cases of status asthmaticus that have resisted adrenaline injections and intravenous aminophylline given four-hourly for twenty-four hours. In most cases of status asthmaticus spasm is relieved by this treatment. Long-acting adrenaline is often not nearly so effective as frequent doses of the simple solution, and intramuscular aminophylline, besides having a much less powerful action than when given intravenously, is very painful and sooner or later will lead to necrotic abscesses.

So far as this country is concerned the therapeutic value of cortisone and corticotrophin in asthma is still *sub judice*. American opinion is much less enthusiastic than it was. Gottlieb,[7] writing from Philadelphia, begins a masterly review of the 1953 literature with these words: "Although no one gainsays the importance of cortisone and corticotrophin as additions to our armamentarium, one senses in the voluminous literature an increasing emphasis on their limitations, on adherence to stricter indications, and on their potential dangers. . . . Few fail to indicate that avoidance of allergens, hyposensitizing injections, and other therapeutic measures are essential for proper management."

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[4] *Lancet*, 1954, **2**, 893.
[5] *Münch. med. Wschr.*, 1954, **96**, 759.
[6] Savidge, R. S., and Brockbank, W., *Lancet*, 1954, **2**, 889.
[7] *Ann. Allergy*, 1954, **12**, 483.

EMERGENCIES IN GENERAL PRACTICE

THE DIFFERENTIAL DIAGNOSIS OF COMA

BY

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Coma is a state of deep unconsciousness from which the patient cannot be roused by ordinary forms of stimulation. There is a total absence of any kind of psychologically understandable response to such stimulation as pinching the skin or vigorous shaking of the patient, but the term "semicoma" is sometimes used to describe those states of less deep unconsciousness in which there may be grimacing or withdrawal movements of a limb on the application of such stimuli.

Importance of an Orderly Approach

There are many possible causes of coma, but for practical purposes a broad distinction may be made between those cases in which coma has supervened as a late development in a patient suffering from a known disease and those in which it is an early and outstanding feature. Greater difficulties in differential diagnosis are likely to be encountered in the latter circumstances, and it is with such cases that this article is mainly concerned.

In dealing with an individual case of coma it is better to adopt a systematic but relatively simple plan of approach as opposed to one which aims at all-inclusiveness at the expense of being unwieldy and unnecessarily lengthy. A scheme based upon the following lines is therefore recommended: (1) An initial consideration of the likeliest causes in the particular patient to be examined. (2) The obtaining, wherever possible, of a history of the events immediately preceding the onset of the coma from any available source—that is, from relatives or witnesses. (3) A systematic physical examination of the patient. (4) A consideration of other less common causes if the underlying disease process is not immediately evident after careful appraisal of all the ascertainable facts.

The causes of coma can be grouped in order of importance as follows:

Cerebrovascular Catastrophes and Conditions Causing Cerebral Ischaemia.—Intracerebral and subarachnoid haemorrhage, thrombosis, embolism, hypertensive encephalopathy, terminal congestive heart failure, severe anaemia due to loss of blood or blood disease, leukaemia, Stokes–Adams syndrome.

Brain injuries, including their complications.

Metabolic Disorders and Endogenous Intoxications.—Diabetes, hyperinsulinism, renal and hepatic failure, Addison's disease.

Post-epileptic States.

Exogenous Poisons.—Barbiturates, carbon monoxide, alcohol, aspirin, arsenic, lead, alkaloids, petrol fumes, carbolic acid.

Intracranial Infections and Tumours.—Meningitis, encephalitis, intracranial abscess, primary and secondary neoplasms.

Physical Agents.—Heat hyperpyrexia, electric shock, caisson disease.

Psychiatric Disorders.—States of severe stupor in hysterical, schizophrenic, and depressive illnesses.

The History

Facts obtained by the interrogation of relatives or witnesses will often provide valuable indications concerning the likely cause of the coma, and may well be indispensable if the patient's previous health has been regarded as good or is unknown to the practitioner.

In respect of antecedent diseases likely to be associated with the later development of coma it will be necessary to make specific inquiries, first, about such conditions as hypertension, cardiovascular and renal disease, diabetes, epilepsy, alcoholism, or drug addiction, and, secondly, with regard to abnormalities of mood or behaviour suggestive of pre-existing psychiatric or organic brain disorders. Thus a history of diabetes will immediately suggest the possibility of either hyperglycaemia or hypoglycaemia, while a history of hypertension or previous strokes will be in favour of a cerebrovascular catastrophe. On the other hand, a history of progressive loss of interest and increasing apathy associated with incontinence of urine may suggest a frontal lobe tumour; a story of recent disturbing emotional experiences in a subject who has previously exhibited hysterical symptoms will lead to suspicions of a hysterical trance state; bizarre behaviour associated with delusions or hallucinations will point to the possibility of the catatonic form of schizophrenia; while a history of increasing retardation coupled with expressions of guilt and self-recrimination or of previous similar episodes will suggest a severe depressive illness.

It must be emphasized that if the patient is truly comatose an organic cause must always be assumed; a state of severe stupor in which there is suppression of voluntary activity but not unconsciousness may be either the antecedent of an organically determined coma or a manifestation of a primary psychiatric disorder.

When coma has supervened in a person whose previous state of health is unknown or has been regarded as good, inquiry will need to be directed towards the circumstances under which it occurred. Indications of likely causes will be obtained if there is a history of recent head injury, haemorrhage, circumstances pointing to a suicidal attempt or exposure to poisonous fumes, or a recent alcoholic bout.

It is important to scrutinize all circumstantial evidence most carefully; sometimes it is seriously misleading. Thus the patient with evidence of head injury may have damaged his head through falling in a stroke, the diabetic is not immune from other disease, the hypertensive may have a cerebral tumour, and the smell of alcohol in the breath is not necessarily indicative of alcoholism. Fortunately, the physical examination will usually help to place such evidence in its correct perspective and should be systematically carried out in every case of coma.

Physical Examination

In the initial general inspection of the patient a search for signs of recent head injury is an important preliminary. Bruising or laceration of extracranial tissues may indicate that the injury is incidental, but bleeding or leakage of cerebrospinal fluid from the nose or ears and subconjunctival haemorrhage spreading forward from the back of the eye usually means a head injury severe enough to have led to a state of coma. The patient's colour should be noted (cherry-red in carbon monoxide poisoning, pale in many types of coma, but cyanotic when the coma is deep whatever its cause), and also the temperature and respiration (shallow in most forms of coma, but deep in diabetes and sometimes "hissing" in uraemia). Sweating is usually pronounced, but is strikingly absent in heat hyperpyrexia. The mouth and

tongue should be inspected for scarring (epilepsy) and pigmentation (Addison's disease), and any tell-tale odours in the breath noted. Lastly, the presence of neck rigidity should be sought and evidence of dehydration looked for.

A systematic survey of function in the various bodily systems should then be made. A brief examination of the nervous system can usually with profit be carried out first and need not as a rule comprise more than a scrutiny of the fundi with an ophthalmoscope, tests of pupillary and oculomotor functions, and a decision on the probable presence or absence of hemiplegia. The presence of the latter is established when it can be demonstrated that the limbs on one side show no movements of withdrawal when pricked, and fall more inertly than their fellows when passively raised and allowed to fall. Changes of diagnostic value that may be seen in the ocular fundi are those of renal or diabetic retinopathy, and the presence (or absence) of papilloedema may be ascertained. The significance of minor inequalities in the size of the pupils is not readily assessed, but a much enlarged pupil on one side showing little or no reaction to light is likely to be due to serious cerebral compression, while a complete unilateral third cranial nerve palsy (closed eyelids, fixed dilated pupil, and abducted eye) is sometimes to be seen in cases of subarachnoid haemorrhage. In all forms of true coma the tendon reflexes will probably be much reduced and the plantar reflexes bilaterally extensor.

In the examination of the cardiovascular system search should be made for evidence of cardiac decompensation, endocardial disease, and irregularities of rhythm, concluding with measurement of the blood pressure. The lungs should be examined for evidence of gross inflammatory or neoplastic disease and the abdomen palpated for the presence of rigidity or abnormal masses. A rectal examination will be necessary if prostatic disease is suspected in a uraemic state; and if early transfer to hospital is impracticable a specimen of urine should be obtained by catheterization and tested for the presence of albumin, sugar, and ketone bodies. Similar considerations apply to lumbar puncture, which will need to be undertaken sooner or later in all cases in which the diagnosis is not obvious; it should not, however, be performed if there is any likelihood that the patient has an intracranial space-occupying lesion.

Differential Diagnosis

The final diagnosis of the cause of the coma in any given instance will depend upon a correct interpretation and synthesis of all the ascertainable facts. In order to assist the practitioner in this task the more outstanding diagnostic features in some of the commoner conditions causing coma are given. Some of these conditions will be considered in more detail in later articles in this series.

Cerebrovascular Catastrophes and Conditions Causing Cerebral Ischaemia

Haemorrhage into brain substance occurs most commonly in late middle life, is usually fatal, and will generally be associated with severe hypertension. Hemiplegia is characteristic of *intracerebral* bleeding and is often associated with stertorous breathing and a slow, full, bounding pulse. The head and eyes are commonly deviated towards the side of the lesion, and retention or incontinence of urine is the rule. In *intrapontine* haemorrhage there is likely to be bilateral limb paralysis associated with pin-point pupils and hyperpyrexia. Spontaneous *subarachnoid* haemorrhage (usually due to rupture of an intracranial aneurysm) generally occurs at an earlier age; in such cases limb paralyses are far less common, but neck rigidity is usually more prominent and there may sometimes be unilateral palsy of the third cranial nerve. Papilloedema and retinal haemorrhages are seen in some cases, and blood is characteristically found in the cerebrospinal fluid; the latter may also sometimes occur in intracerebral bleeding, but in such cases the presence of hemiplegia and a more deeply comatose state are helpful diagnostic features.

When coma occurs in cases of *cerebral thrombosis* it is usually less profound and of more gradual onset than in the case of intracerebral haemorrhage. Hemiplegia is often present, but hypertension is less common and there may be a history of previous strokes. An onset with sudden severe headache or vomiting is much more in favour of intracerebral haemorrhage than of thrombosis.

Coma is of uncommon occurrence in *cerebral embolism*. A semicomatose state may occasionally be encountered when there is occlusion of a large vessel such as the middle cerebral artery; diagnosis in such cases depends upon establishing the association of sudden unconsciousness and accompanying neurological signs (hemiplegia) with the presence of a cardiac or pulmonary lesion likely to be a source of emboli (coronary thrombosis, endocarditis, auricular fibrillation or flutter, pulmonary infarct, or suppuration).

Hypertensive encephalopathy may complicate benign or malignant hypertension, acute nephritis, and eclampsia. There is usually a subacute onset consisting of transient focal cerebral disturbances (amaurosis, aphasia, hemiplegia) followed by the development of convulsions and coma. The blood pressure is always raised, especially in malignant hypertension, when the diastolic reading is usually in the neighbourhood of 130–150 mm. Hg; papilloedema with or without the exudative changes of hypertensive retinopathy may be present in some cases, and urinary changes will be found when there is acute or chronic renal damage. The focal cerebral disturbances are much more transient than those occurring in cerebrovascular lesions, and the usually good response to treatment (venesection and lumbar puncture) may be a helpful diagnostic feature.

Brain Injuries

The patient remaining in a state of coma after the receipt of a head injury must be presumed to have sustained either a *contusion* of his brain or an injury complicated by *intracranial bleeding*. The latter is particularly likely if the patient has recovered from the immediate effects of the injury and subsequently lapses into deepening unconsciousness. This indicates increasing cerebral compression and will be associated on the side of the haemorrhage with a progressively dilating pupil which fails to react to light.

A history of relapsing impairment of consciousness ranging from drowsiness to coma suggests a *chronic subdural haematoma* which is usually a complication of a comparatively mild head injury, although such a history may sometimes be lacking. Males are much more commonly affected than females, and localizing signs are slight or absent until a late stage, although a dilated pupil is often found on the side of the haematoma.

Metabolic Disorders and Endogenous Intoxications

In *diabetic coma* the onset is gradual and follows a period of severe ketosis (dyspnoea, anorexia, nausea, vomiting, drowsiness, and diffuse abdominal pain). The patient is dehydrated and collapsed, acetone is present in the breath, and the tests for sugar and ketone bodies in the urine are strongly positive.

Coma of *hypoglycaemic* origin is always of rapid onset. Convulsions often occur in the early stages, and it is distinguished by the absence of both dehydration and ketonuria. Focal neurological signs (hemiplegia) may sometimes be present and sugar is occasionally found in the urine.

Coma due to *renal failure* is characterized by dehydration and dyspnoea associated with muscular twitching, convulsions, and albumin-laden urine of low specific gravity.

In cases of coma due to *hepatic failure* ("*cholaemia*") there is an antecedent phase consisting of malaise and jaundice followed by drowsiness, delirium, vomiting, muscular twitching, and a tendency to haemorrhage.

Post-epileptic Coma

This is only likely to be a serious problem in the presence of status epilepticus. Focal neurological signs may or may not be present, but in the absence of an antecedent history of epilepsy there will sometimes be evidence of previous tongue-biting. Both albumin and sugar may be found in the urine

and some degree of pyrexia is usual. Occasionally coma in an epileptic subject may be due to overdosage with anticonvulsant drugs.

Exogenous Poisons

Here the diagnosis will usually depend primarily upon circumstantial evidence and the exclusion of other causes of coma. Special features to be noted are the cherry-red complexion in *carbon monoxide* poisoning; the smell of stale alcohol in the breath in *alcoholic* poisoning; the association of fits, raised blood pressure, and a "lead line" in the gums in lead *encephalopathy*; the hyperpnoea and violet urinary ferric chloride reaction in *aspirin* poisoning; and the normal or subnormal temperature and pin-point pupils in *opium* poisoning.

Intracranial Infections and Tumours

Meningitis in its various forms can sometimes be a cause of rapidly developing coma, especially the fulminating *meningococcal* variety. Diagnostic difficulties may nevertheless be considerable when the temperature is subnormal and neck rigidity is inconspicuous. A purpuric rash is commonly present in meningococcal infections, while in other forms there may be a focus of infection elsewhere in the body. Usually, however, the diagnosis can be established only by lumbar puncture.

In cases of *localized intracranial abscess formation* coma is likely to be a late event. Headache of increasing severity and drowsiness are outstanding premonitory symptoms, mastoiditis and intrathoracic suppuration being the commonest sources of infection. Occasionally coma supervenes rapidly if the abscess ruptures into the cerebral ventricles or subarachnoid space, in which case there will be neck rigidity associated with high temperature.

Coma is also usually a late development in cases of *intracranial tumour*, whether it be primary or secondary in origin. Occasionally it may develop rapidly when there is cystic degeneration or haemorrhage into a tumour, but differentiation from intracerebral haemorrhage is usually impossible on clinical grounds alone.

Physical Agents

Heat hyperpyrexia is a serious condition due to failure of the heat-regulating mechanism as a result of prolonged exposure to high temperatures. It is usually fatal without adequate treatment and is characterized by progressive hyperthermia, absence of sweating, convulsions, circulatory collapse, and coma.

An individual accidentally subjected to the *effects of an electric current* may be rendered comatose. Diagnosis will depend upon the detection of skin burns and a consideration of the circumstances.

Mental Disorders

Severe states of stupor occurring in hysterical, schizophrenic, or depressive illnesses may sometimes give rise to diagnostic difficulties. In cases of this kind the patient is not likely to be truly unconscious, since he may show some evidence of mental activity or betray the fact that he is not entirely unaware of his surroundings. Diagnosis will depend upon the absence of physical signs and evidence of psychological disturbance in the history obtained from friends or relatives. Organic disease must be assumed to be present, however, if the patient is genuinely comatose, even if there is a history suggestive of mental disorder.

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PROFESSIONAL BOXING AND THE DOCTOR

BY

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In an editorial comment in the *British Medical Journal* of December 25, 1954 (p. 1535), the hope was expressed that the controlling body of professional boxing would listen to the advice of its medical advisers.

In order to show that the professional controlling body does, in fact, listen to its medical advisers, I propose to give a short account on the control of professional boxing, with special reference to the medical aspects of professional boxing.

Prior to 1929 the control of professional boxing in the British Isles and on the Continent was practically nonexistent. Owing primarily to the efforts of the late Lord Lonsdale, the British Boxing Board of Control was formed in that year. Lord Lonsdale became the first president. The constitution of the Board is a president, two vice-presidents, and a number of stewards, all of whom have some specialist knowledge of boxing and are not in any way financially interested in boxing. The stewards serve in an honorary capacity and meet their own expenses. Should a vacancy occur, it is filled by invitation from the president and the stewards.

An account of the ups and downs of the Board of Control from 1929 to the present time, although interesting, would be out of place here, but a short account of the present organization is necessary.

Organization of the Board of Control

The Board now consists of a president, two vice-presidents, and up to 25 stewards, divided into stewards of appeal and administrative stewards, and has through its regulations complete control of all professional boxing in Great Britain and Northern Ireland, except fairground boxing booths. It has the authority to issue licences at its absolute discretion to all persons connected in any way with professional boxing (boxers, promoters, managers, referees, trainers, seconds, etc.). Without a current licence no one can officiate in any capacity at a professional boxing tournament.

The Board functions from head offices in London and is assisted by eight area councils covering the whole country and Northern Ireland. The area councils are made up of licensed members of various categories—promoters, boxers, boxers' managers, seconds, etc., elected annually by the licensed members in the area. Each area council has two representative stewards, who are elected annually by the council members, and who represent the views of their councils to the stewards at board meetings.

Before the second world war the medical arrangements were rather sketchy. A principal medical officer was appointed who was one of the administrative stewards. His main duty was to advise the Board on any medical matter which cropped up and to examine boxers where necessary on behalf of the Board.

During the second world war the control of boxing suffered, as most of the stewards were engaged in one or other of the Services. After the war, when the Board got into its stride again, it was quickly realized that a medical organization was a necessary part of the controlling body, and by 1950 such an organization was instituted as follows. An honorary area medical officer was appointed to each of the

eight areas. These medical officers, together with any medical men who happened to have been elected as representative stewards, constituted a medical subcommittee under the chairmanship of an administrative steward, who is also a medical man. Since 1951 it has been found necessary to appoint one or more deputies to the area medical officer in each area.

Since the formation of the medical subcommittee, its recommendations have been implemented without question by the Board of Control. Further, owing to the efforts of the president of the British Boxing Board of Control, the European Boxing Union was formed in 1950. This controls professional boxing throughout Europe, and is served by a medical commission elected from the principal medical officers of member countries.

The objects of the medical subcommittee are to advise the stewards on medical matters and how to make boxing freer from the isolated instances of permanent injury, particularly the results of brain injury. Some of the medical aspects of professional boxing which have been dealt with by the medical subcommittee are:

1. Medical Examinations

Every applicant for a boxer's licence is subject to a comprehensive medical examination, the results of which are reviewed by the area medical officer, who then recommends the granting or withholding of a licence. The boxer must be medically examined before and after every contest.

If a boxer has been knocked out he must be medically examined before contracting to box again. Medical officers, promoters, seconds, managers, council members, or area secretaries can insist that a boxer be medically examined at any time there is reason to think he is suffering any brain injury. Unless the boxer receives a certificate of absolute fitness from the area medical officer, his licence is suspended for a varying period or withdrawn altogether.

Only first-series—that is champion or near champion—professional boxers are allowed by the Board to box outside the British Isles, and by agreement with other members of the European Boxing Union each must be medically examined by an official medical officer and certified fit immediately before leaving for abroad. All licensed referees are examined annually before their licence is renewed, because to referee several contests during the course of an evening requires a fit man.

2. Various Recommendations Made by the Medical Subcommittee and Implemented by the Stewards

Action to be Taken by Seconds After a Knock-out.—The theory has been advanced by various observers that there are two kinds of knock-out, and experience seems to bear this out. They are adequately described by La Cava (1952), who classifies them as (1) a reflex from a hard blow on the chin, and (2) a final loss of consciousness as a result of a blow when a boxer has reached a state of collapse due to a number of blows. Managers, seconds, etc., are now instructed in words of two syllables how to treat an unconscious boxer by the first-aid methods applicable to any other case of concussion, always bearing in mind the possibility of more serious damage. Ear rubbing, strong smelling-salts, and any form of stimulation are expressly forbidden.

Haemostatics.—Formerly it was the custom for each manager or trainer to have his own particular solution to stop bleeding from a cut sustained during the course of a contest. Many of these, whilst achieving the end desired by the managers or trainers, resulted in serious tissue damage. Nowadays it is an offence for anyone to use a substance which has not been approved by the medical subcommittee. Many substances have been examined, the only one approved at present being adrenaline solution. If adrenaline solution will not control the haemorrhage, then the contest is either abandoned by the manager or stopped by the referee.

Stimulants.—No form of stimulant, either real or imaginary, is allowed by the Board, except cold water sprinkled on the body or used as a mouth wash.

Drying Out and Weight Reduction by Turkish Baths.—In the past, matches were made for a boxer at a weight which was often below that at which he was 100% fit and strong. This weight was achieved by withholding all fluids for, in some cases, up to 48 hours before the weigh-in, and by turkish baths. On the recommendation of the medical subcommittee, because of their weakening effects, these practices have been stopped and managers' licences have been withdrawn for indulging in them.

Blows to the Kidneys and Back of the Head.—The original rabbit punch, barred by the rules of boxing for many years, was a chop with the side of the hand to the back of the neck, and a similar chop was delivered over the kidney region. Either of these blows has for many years resulted in the instant disqualification of the boxer who delivered them. On the recommendation of the medical subcommittee, because of the risk of brain or kidney trauma, blows with any part of the fist to the back of the head, or to the region of the kidney, are deemed foul and referees have been instructed to see that their use is stopped.

Duration of Contests.—These have been standardized for various classes of boxers and the duration reduced to eight minutes' actual boxing for novices.

Eye Injuries.—Serious eye injuries are extremely rare. Visual standards have been fixed so as to prevent a myope being licensed, to reduce the risk of a detached retina.

Many instructions covering minor points of the medical aspects of boxing have been issued dealing with widely separate subjects such as the correct position to hold the hand within the glove, scabies or infectious skin diseases in boxing stables, and the best method of suturing cuts. The prevention of fatal accidents or permanent brain injury to boxers remains the main problem facing the medical subcommittee.

Fatal Accidents

Much has been done in this connexion. Since the war there have been five fatal accidents to professional boxers at licensed promotions. Death in all these cases, as indeed it has been in the cases reported from abroad, was due to haemorrhage from cortical veins. No case of a fractured skull has been reported. The type of injury—tearing of the cortical veins—and the history lead to the conclusion that the injury in most cases was caused not by the blow but by the boxer striking the back of his head on the ring floor, causing an abrupt deceleration of the brain mass. With this in mind, the medical committee has recommended that a special type of ring flooring developed by Cornell University, U.S.A., be obtained and tried out in this country. In the meantime, some resilient substance, such as sponge rubber, is put under the canvas of all rings.

Permanent Brain Injury

Before the days of an adequate control, an appreciable percentage of professional boxers suffered from a condition known among themselves as being "punch drunk." This condition is also met with in some steeplechase jockeys and amateur riders who have had more than a fair proportion of falls in the hunting-field or steeplechasing. The term "punchy" was often used of a boxer as an expression of contempt. Because of the stigma attaching to the name it was decided to substitute the term "chronic concussion" whenever it had to be referred to. The signs and symptoms of an established case have been frequently described by various observers. Agreement regarding the pathology, however, is not by any means unanimous. What is obvious, however, is that, as a result of a series of concussions, the brain does receive damage which, if severe, is irreversible, but which if detected in the early stages seems to clear up. In the absence of any specific treatment, it is the obvious

duty of the medical subcommittee, through the Board of Control, to prevent its occurrence, and this is being done in the following way.

All licensed referees are lectured by the area medical officer on the medical aspects of boxing, with particular reference to chronic concussion. They are instructed that they must not allow a boxer to take unnecessary punishment, and must, under no circumstances, allow a defenceless boxer to be struck. Flagrant disregard of this warning by a referee will result in his losing his licence, or being suspended for a varying period, or being degraded to a lower category of referee. During 1954, in implementing this instruction, 360 contests out of 1,973 were stopped by the referee before either a knock-out or the end of the contest had occurred. One curious result of this is that the spectators at any boxing tournament now protest vociferously if the referee in their opinion does not stop the contest soon enough.

Professional boxers have a hard system of training to follow, which, amongst other things, involves sparring. Brain injury can occur in the gymnasium as well as in the ring. All managers, trainers, promoters, and others connected with professional boxing are instructed, in the boxers' interests, to report at once any early signs of chronic concussion. The relatives and those associated with a boxer in training are the ones who notice some slight abnormality before it is detected in a normal routine examination. Obviously, area medical officers, deputy medical officers, and tournament medical officers are constantly on the lookout for any early signs of chronic concussion. Once a boxer is suspect, he is ordered to be examined by the area medical officer, and unless he is given a complete clearance his licence is withdrawn or suspended. During 1954 19 licences were withdrawn or not renewed on medical grounds. The reason for the withdrawal is explained to the boxer, and he is advised to abstain from any form of sparring in the gymnasium until given a clearance by the area medical officer.

It was thought that electroencephalography might be a means of diagnosing early chronic concussion. In this connexion the results recently published by Kaplan and Browder (1954), who spent four years studying the brain-wave patterns of 1,043 professional boxers, are disappointing, a disorganized E.E.G. showing at most that a complete physical and neurological survey is indicated.*

Conclusion

The aim of the Board is better and safer boxing. To this end they will implement any reasonable recommendation of the medical subcommittee. It is due solely to the efforts of the present president of the Board that the European Boxing Union, of which he is also the president, is in existence and that it has a medical commission. Further, again owing to his efforts, a World Boxing Union was formed consisting of a representative from the New York State Athletic Commission, one from the European Boxing Union, one from the National Boxing Association of America, and one from Great Britain and the British Empire. This World Boxing Union has, in its turn, appointed a medical advisory board.

Finally, the medical subcommittee of the British Boxing Board of Control will be grateful for any suggestion, from any medical man interested in this pre-eminently British sport, that makes for safer boxing.

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*Of the 1,043 subjects, 197 had repeated electroencephalographic examinations varying in number from 1 to 6. The interval between examinations was less than one year in 141 subjects, between one and two in 29, between two and three in 21, and between three and four in six. Forty subjects had the examination repeated within 10 minutes of losing a contest. Ringside cinematography (slow-motion and ordinary) was used to assess the type and extent of trauma to the head.

PROFESSIONAL NEGLIGENCE

LECTURE BY A QUEEN'S COUNSEL

At the City of London College on January 12 Mr. J. P. EDDY, Q.C., delivered the first of a series of Travers Memorial Lectures on "Professional Negligence." He said that the main principle he was about to put forward was that before there could be negligence there must be a duty to take care or to exercise reasonable skill. That duty might arise in one of two ways: (1) in common law (as, for example, to exercise reasonable care when driving a car), and (2) under contract, as in the relationship of doctor and patient.

Three elements had to be considered when dealing with common law liability. The first was a duty to exercise care or skill or both; the second, a breach of such duty; and the third, an actual loss to the other party as a result of such breach. The late Lord Macmillan had pointed out in a case in 1932 that the law took no cognizance of carelessness in the abstract; there must be carelessness when there was a duty to take care, and it must be proved that failure in such duty caused damage. When there was a contractual relationship negligence might be a breach of such contract by act or omission.

Responsibility of the Professional Man

A man or woman who practised a profession was bound to exercise care and skill—the skill of an ordinary competent practitioner in that profession, whether it be of accountant, banker, solicitor, or doctor. The important principle had been laid down that every person who entered a learned profession undertook to bring to its exercise a reasonable degree of care and skill. He did not undertake, if he was an attorney, that his client should win his case, or, if he was a surgeon, that he would cure his patient; nor did he undertake to use the highest degree of care and skill of which some persons in his profession might be capable, but he undertook to bring to the case a fair and reasonable competence. It followed, therefore, that where the duty to exercise care and skill existed one of two things might give rise to an action for damages for negligence: (1) that the defendant did not possess the requisite skill, or (2) that, although he possessed it, he did not exercise it in the particular case.

In some cases an action might arise out of tort at common law—that is, neglect of a duty towards persons generally; in others it might arise out of contract—that is, an agreement between the parties whereby there arose a duty to exercise a reasonable degree of care and skill; and sometimes there might be an overlapping of tort and breach of contract. But the first essential was to recognize that before there could be a liability there must exist a duty—a duty in the case of a professional man to show the average amount of competence associated with his profession. The expected degree of competence varied with the times. Two generations ago surgical operations were conducted in a manner which, by the standards of our own time, would be accounted negligent.

What Constitutes Negligence?

Mr. Eddy went on to point out that in a contract as between doctor and patient only those two people were concerned; only the partners to a contract, one or other of them, could complain if there was negligence.

A person who was himself under a duty to take care could not get rid of his responsibility by delegating the performance to someone else. He was answerable for the wrongful act of his servants or agents committed in the course of their employment. The principle of vicarious liability for the wrongful acts of others rested on the legal maxim, *Qui facit per alium facit per se* (he who does anything by another does it himself). But the wrongful act must be done in the course of employment. If a doctor employed a dispenser who, while dispensing, spilt some liquid over a patient and injured him or damaged his

clothing, the doctor was liable. If, however, the dispenser was entertaining a friend in her own room and upset some hot water over her and scalded her, the doctor was not liable. Where the servant or agent was negligent in the course of his employment, then *Respondeat superior* (let the principal be held responsible).

That principle came into its own in the case of Cassidy *v.* Ministry of Health (1951, 2 K.B., p. 343). He took it as good law and good sense when Lord Justice Denning (and there was no dissenting judgment) declared that where a person was himself under a duty to use care he could not get rid of his responsibility by delegating the performance of it to someone else, no matter whether the delegation be to his servant under a contract of service or to an independent contractor. The Cassidy case supported the principle that if a patient in hospital suffered injury through the negligence of some member of the staff it was unnecessary for him to pick upon any particular employee. The law applied the principle *Respondeat superior* in the case of a hospital and its staff just as it did in the relation of master and servant in any other sphere of activity, professional, industrial, or other. It mattered not that the servant did work of a skilful character for which he was specially qualified. The hospital was responsible for all those in whose charge the patient was. It had taken the law over 30 years to reach this position, owing, Lord Justice Denning had suggested, to the feeling that charitable institutions should be relieved of a liability they could not afford. But the National Health Service Act, 1946, had altered the status of hospitals, and, speaking generally, it had brought about a change in the attitude of the public towards them.

In the case of Cassidy the plaintiff entered the hospital for an operation which involved post-operational treatment. At the end of the treatment it was found that his hand had been rendered useless. It was held *Res ipsa loquitur* (the thing speaks for itself), and the onus was laid upon the hospital authorities to prove that there had been no negligence on their part or on the part of anyone for whom they were responsible. The principle *Res ipsa loquitur* had been applied in other negligence actions, in particular in an action against an anaesthetist and actions against two dentists.

The Increased Litigation Against Hospitals

Negligence, summed up Mr. Eddy in conclusion, involved a breach of the duty to exercise reasonable care and skill. Such a duty might arise out of tort—that is, it might be a duty fixed by the common law—or it might arise out of contract, and where it did so arise it was a duty existing only between the parties to the contract. But, whether it arose out of tort or out of contract, the person concerned was answerable for the acts of his servant or agent if such acts were done in the course of his employment.

It was the extended application of this principle which explained the recent remarkable increase in litigation concerning the liability of hospitals in cases of alleged professional negligence. The substantial increase in the volume of litigation against hospital authorities in recent years was strikingly illustrated by the fact that in 1948–9 the payment made by hospital authorities in England and Wales in compensation of all kinds amounted to £7,500, and in 1953 it had risen to £153,000.

Mr. Eddy promised to deal with other aspects of this question in a future lecture.

The Royal Australian Air Force is in great need of additional medical officers, and the attractive terms of service have recently been outlined in advertisements in this *Journal* (December 11, 1954, advertisement page No. 27). Doctors who join the R.A.A.F. in this country are paid from the date of embarkation and given free first-class passages to Australia for themselves and their wives and families. Provision is made for postgraduate training in R.A.A.F. and civilian hospitals in Australia.

Reports of Societies

PALLIATION IN CANCER

On January 5 at the Royal Society of Medicine the Section of Surgery, with Sir HENEAGE OGILVIE in the chair, held a discussion on palliation in cancer.

Mr. H. T. SIMMONS (Manchester), who opened the discussion, said that the treatment of cancer was becoming so complicated that he would limit his remarks to the more common types. Although treatment of operable cancer was a technical exercise that could be learned fairly easily, the treatment of inoperable cancer was more complicated and needed more judgment. Surgeons were often guilty of putting an inoperable case at the end of a long operating list, and the assessment of the real needs of the patient was often equally superficial. Clear thinking rather than skill was required. Colostomy, for example, should rarely be inflicted on patients over the age of 70 with inoperable rectal carcinoma, since they were thereby made more miserable. Heroic surgery was of doubtful value and seldom justifiable. Adrenalectomy and hypophysectomy had a place in the treatment of endocrine-dependent growths, but only half the patients got significant relief and they then became dependent on a scarce and expensive drug. These operations should not be used indiscriminately. Perhaps in the future suppression of hormones by medical means would be preferable.

Palliative Surgery

Prolongation of life should not be the only consideration in patients with inoperable growth : relief of pain and of the effects of bowel obstruction or the clearing of foul discharges was equally important. The presence of metastases should not contraindicate local treatment which would bring about relief of symptoms. But short-circuit operations which did not relieve pain and discharge probably did more harm than good. Metastases giving rise to symptoms could often be removed: in such cases radiotherapy was often disappointing. In the elderly, local excision of breast tumours often relieved the pain and removed the source of offensive discharge. Skin cancer called for palliative treatment only when the face was affected : then, deep cavities should be opened up and diathermy excision applied. If this was followed by expert prosthesis encouraging results were often obtained. In carcinoma of the oesophagus gastrostomy was inadvisable, since the accumulation of saliva and inability to swallow was the most distressing symptom. Many gastric carcinomas were inoperable when first seen, and careful pre-operative assessment would avoid many unnecessary operations. It was doubtful if palliative gastroenterostomy was ever justified; it was better whenever possible to remove the growth. Anastomosis of the gallbladder to the duodenum was often a satisfactory operation in patients with carcinoma of the bile passages. The help from hormonal therapy in prostatic carcinoma was remarkable ; the results obtained were often better when orchidectomy was done at the same time. Similarly, before the menopause, testosterone gave good results in mammary carcinoma, but the patient often resented the masculinization which followed. After the age of 60 oestrogens were more beneficial.

A Physician's Viewpoint

Dr. C. J. GAVEY (London) enunciated some broad principles in the treatment of patients with inoperable cancer. There was need for hopefulness to the end. It was most important to relieve pain, because when pain disappeared the patient's morale improved. Popular opinion wrongly held that cancer was always painful, but patients who had recovered from cancer often remarked on the lack of pain. Assessment of the degree of pain was never easy, but it was especially difficult for young doctors and nurses who lacked experience. When pain was present analgesics should be

given continuously. Mixtures with aspirin and opium could be given every four hours; and drugs of addiction were seldom contraindicated as such. Pethidine had advantages over morphine, because it did not depress the patient so much. Methadone was valuable, but might cause trouble by suppressing the cough. Phenadoxone had a long action and was of value. Chlorpromazine was of most value when vomiting was present, but it was better to reduce the dose when vomiting ceased. R 48 often abolished pain from hepatic secondaries. Morphine was most useful in the terminal stages and should never be spared. It was, however, sometimes difficult to know when to start using morphine. It was wise not to exceed single doses of ¼ gr. (22 mg.).

The second difficult problem was that of telling the patient about his illness. Patients did not share the doctor's knowledge of disease and did not therefore appreciate how patients with cancer died. When patients persistently asked for information it was morally wrong to suppress it. Frequent visiting helped in knowing when to tell the patients about their illness. The power of self-deception might be very great, and it behoved the doctor to promote this at all times. Most patients accepted the truth if it was realized slowly. There was no place for a deliberate lie or for complete silence. The problem was more difficult with intelligent patients, to whom frankness must be shown if it was sought. Medical patients themselves were often bravest and most serene when they understood their own illness. Frequent visits to the patient were fundamental, and it was the doctor's duty to help his patients in this way. It was salutary to ask if one paid sufficient attention to prevent the patient wondering if the doctor had lost interest in his case. The nursing staff were also helped by the doctor's visit, and the task of the relatives was made more simple. Sympathy by relatives was often best shown by being practical. Of paramount importance was the employment of surgery and radiotherapy. Adrenalectomy was an operation that had come to stay, especially in those cases of breast cancer with bone secondaries and pain. Requests for further opinions by the patient must be met with sympathy even if the patient wished to venture into the fields of unorthodox therapy. In the terminal stages of the disease it was wise to see that spiritual help was available to the patient.

The Role of the Neurosurgeon

Professor NORMAN DOTT (Edinburgh) said that the neurological surgeon might assist in the palliation of cancer in four several ways: (1) When he encountered metastatic cancer of the brain while the nature of the disease was still in doubt—he made the diagnosis. (2) When called upon to assist in ameliorating the course of the known neoplasia by hypophysectomy. (3) When requested to mitigate pain in known cancer. (4) When called upon to preserve important neural functions threatened by known cancer.

He pointed out that metastatic cancer of the brain had notably increased in frequency in recent years in proportion to the increase in bronchial carcinoma. In all patients over 30 years of age, with rapidly progressive cerebral tumours, an *x*-ray picture of the chest and other means of search for a primary pulmonary lesion were routine procedures. Not infrequently, however, the cerebral metastasis was the first recognizable lesion in this disease. When the diagnosis was made by exploration of the cerebral lesion, or by any other means, the advice of the oncologist on the management of the neoplasia as a whole was sought.

The oncologist was usually the radiotherapist, who usually had the largest experience of neoplasia in its many sites and in its various stages of evolution. An oncological team might be desirable with the radiotherapist as its leader, and with the pathologist and endocrinologist associated and other specialists called in as required. It had become essential for "system specialists," such as the neurological surgeons, to have available the advice of an oncologist on the management of the neoplastic malady as an entity, when a metastatic manifestation of it was encountered in the brain.

In the management of cancerous neoplasia it had been found that in the parasexual tumours—those of the breast and prostate—modifications of the sex hormone state might profoundly modify the progress of the disease. Administration of oestrogens and of androgens, or their diminution by castration, adrenalectomy, or hypophysectomy had been employed. Whether hypophysectomy had special indications or advantages was not yet known. Neurological surgeons stood ready to join the oncological team as assistants if hypophysectomy proved of special value in the management of cancer.

Professor Dott thought that pain due to cancer could and should be abolished in those cases in which it constituted a clamant symptom. Pain was a sensory experience and also an emotional experience—a distress. Conscious appreciation of pain as a discriminatory sensation was a function of the cerebral cortex. Conscious appreciation of the distressful aspect of pain was a function of the diencephalon. When pain was judged to be an important factor it might be mitigated by psychological methods, by analgesics, or by surgery.

Relief of Pain by Neurosurgery

Surgery for pain took two main forms: (1) Interruption of the pain-conducting pathways, so that the pain stimuli were prevented from reaching consciousness. (2) Modification of consciousness or personality on its affective aspect by leucotomy so that the distressful element of the pain experience was lessened or abolished. Surgery for pain was justified when there was a life expectancy in excess of three months and when pain was a major factor in the patient's total distress.

Instances of satisfactory interruption of pain pathways were: trigeminal nerve interruption for cancer of the face, to which could be added interruption of the glossopharyngeal, upper vagus rootlets, and upper cervical posterior roots when the floor of the mouth and throat were involved; spinothalamic cordotomy at segmental level D 2 for pain below waist level, and at C 2 for pain up to arm level. For disease about the thoracic inlet one could combine a C 2 cordotomy with section of the upper cervical posterior roots. The techniques of these operations were discussed. It was noted that, while eminently successful in dealing with pain, their usefulness was limited to its abolition—they did not benefit other forms of distress which were often important in the cancer patient.

Leucotomy had the advantage of mitigating all forms of distress—not only those due to pain. It did not abolish physical pain sensibility, but it abolished its distress. This relief was necessarily bought at the expense of a diminished affective depth of the whole personality, and was therefore limited to those cases in which this was considered justifiable. A somewhat similar effect was procurable by large doses of chlorpromazine. There had not yet been opportunity for prolonged trial of this remedy.

Neurological surgery was required on occasion to preserve important neural functions threatened by cancer. Cranial decompression, with or without removal of a cerebral metastatic growth, could preserve vision and relieve headache and vomiting. Spinal decompression could avert paraplegia with all its distressing accompaniments. When indicated by the early symptoms of spinal cord compression, it was an operation of urgency. It could be supplemented by stabilization of the vertebral column by the implantation of rustless steel plates, if the vertebral bones were weakened by cancerous erosion.

Thus neurological surgery could play its part in the diagnosis and treatment of cancer, and in the mitigation of pain and preservation of function, even in the "hopeless" case.

Management by the Family Doctor

Dr. G. F. ABERCROMBIE (London) spoke of the difficulty in managing inoperable cases of cancer and of the problem of what the patient should be told. It had to be realized that a stage arose when surgical treatment should cease, and the practitioner was often the best person to decide on this.

Morphine helped these patients, and it had been said that "morphine exists to be given and not merely to be withheld." The increasing nursing supervision required in the terminal phases often became impossible in the patient's home; it was the duty of hospitals to readmit their patients in this phase. Surgeons often deceived the patient in the matter of diagnosis and put the general practitioner at a disadvantage. Many patients were left in ignorance to the end, but it was doubtful if this was advisable. It was a mistake not to give patients the credit for the common sense and courage they possessed. Doctors were often afraid to tell patients about their disease.

Many fallacies about cancer needed correcting. It was remarkable that many patients with cancer died with much less distress than patients with heart failure. Patients with cancer were often more content when the diagnosis was known and the relatives were spared the unhappiness of constant deceit. Dr. Abercrombie had never regretted having told a patient about cancer. The bond between the doctor and the patient was thereby strengthened and remained firm to the end.

Discussion

In the discussion that followed, Professor C. A. WELLS (Liverpool) suggested that the problem of palliating cancer had so many aspects that no one man could be expected to be familiar with all the methods or even to be competent to select the appropriate method or combination of methods in any one case. In these circumstances the difficulty might best be met by organizing a group of workers to consider jointly or in the closest possible consultation the problems involved. Indeed, he thought it probable that this type of approach was appropriate not only to the cancer problem but to a number of other states, such, for example, as arterial hypertension, in which many voices might need to be heard before an appropriate line of treatment could be decided upon and in which subsequently there might be a need for guidance from many points of view. By an extension of the same argument it was permissible to ask whether there should not be a tendency for these and other most difficult cases to move from the periphery towards the centre of various regions of surgical organization to secure for them the best advice and treatment.

Mr. MURRAY FALCONER (London) said that although hypophysectomy for parasexual tumours was in its infancy it was an operation with a low mortality and it appeared to help more than half the patients. Metastases often disappeared, but, as the follow-up periods were still short, it was not yet possible to compare it with adrenalectomy. These encouraging results made it difficult to say that there was ever a stage when treatment should be denied because the disease had become advanced and widespread.

Many other members and visitors took part in the discussion, and it was clear that varying views were held about what to tell the patient suffering from inoperable carcinoma.

LOCAL MEDICAL SOCIETIES

Liverpool Medical Institution

Addressing the Liverpool Medical Institution on December 16, 1954, on a medical pilgrimage "from the Cape to Cairo," Professor L. S. P. DAVIDSON said there were certain diseases which were much rarer in Africans than in Europeans living in the same region. They fell roughly into two large groups: (1) the so-called psychosomatic diseases such as peptic ulceration, thyrotoxicosis, essential hypertension, and rheumatoid arthritis; (2) degenerative vascular and metabolic disorders such as atheroma (and its sequence of coronary and cerebral thrombosis, and peripheral vascular disease), cholelithiasis, and diabetes mellitus. The relative rarity of these diseases might be due either to racial or constitutional causes, or to environmental causes. But, if it were true that Africans who have adopted Western methods of eating, working, and living became as liable to these conditions as Europeans, then environmental rather than racial factors would appear to be of primary aetiological importance.

Correspondence

Because of the present high cost of producing the Journal, and the great pressure on our space, correspondents are asked to keep their letters short.

Fluoridation of Public Water Supplies

SIR,—Dr. C. G. Dobbs (*Journal*, January 8, p. 105) describes the proposal to add fluoride to the water supplies in Anglesey as undoubtedly amounting to "compulsory medical treatment with a toxic substance intended to produce a physiological change in the body, to be administered indiscriminately by medically unqualified persons." He goes on: ". . . no individual doctor can be discovered who claims to know much about its effects, or to be able to diagnose slow chronic fluoride poisoning if it should occur. If this is the situation the 'experiment' could do widespread damage without anyone's being the wiser."

As a member of the independent mission which investigated American experience with fluoridation and reported to the Ministry of Health, the Medical Research Council, and other interested bodies, perhaps I may be allowed to comment. The mission, in its report,[1] felt justified in drawing four main conclusions. First, there is abundant evidence, from Britain as well as America, that lifelong consumption of water containing fluorides at levels around 1 part per million results in a substantial reduction of the incidence of dental caries in children, and probably in adults also; in view of the prevalence of the disease, the shortage of dental manpower, and the absence of any other practicable preventive measure, the benefits of fluoridation (adding fluoride at a level of 1 p.p.m. to waters not naturally so endowed) are of great value. Secondly, there is no scientific evidence whatsoever that fluoridation involves any danger to health, and very considerable evidence that it is harmless. Thirdly, the amounts of fluoride added to water can be controlled very accurately. Fourthly, evidence derived from the millions of people in Britain and abroad, who use waters containing about 1 p.p.m. of fluoride, naturally present, is wholly reassuring both as to the absence of danger and as to the benefits resulting. It may be noted here that one of the earliest British reports[2] on dental benefits related to children evacuated during the war from a natural-fluoride area; the school dentist in the reception area was impressed by the fact that they had "remarkably good teeth—much better than those of the local children."

Dr. Dobbs uses the term "medical treatment" for a measure which does not *cure* dental caries but helps to prevent it. I will not indulge in what he calls "verbal quibbling," but it seems necessary to remark that, in the lay press, he has written: "The compulsory mass-medication of people via the public water-supply is the sort of thing which has not been tolerated by civilized European opinion, or practised in Europe, so far as I know, outside the concentration camp (at least until very recently)." This is the kind of highly coloured and unscientific language which is best avoided in debating the factual merits of a case. The ethics of compulsion, of course, are always good for heated argument, as is shown by the whole history of advance in public health; in the present instance, I should like to make it clear that no alternative to public water supplies as a vehicle for fluorides can at present be advocated on technical grounds or on those of safety.

It seems scarcely necessary to point out that fluorides will not be "administered indiscriminately by medically unqualified persons." The word "indiscriminately" ill describes a process which will be conducted with strict administrative, mechanical, and chemical controls, and supervision will, of course, include that of the medical officer of health. Variations in the amounts of fluoridated water ingested by individual consumers are known to be without significance for health, within the very wide range of climates in the North American continent. Variations of consumption are

almost certainly less in this country, and the question of individual intakes of fluorides has been closely examined. There is no risk that, in the unprecedented event of fluoridation causing damage to health, this will occur "without anyone's being the wiser." The arrangements in Anglesey and other areas where the water is about to be fluoridated will be subject to regular scrutiny by doctors and dentists who know the signs of fluorosis. It is not surprising that Dr. Dobbs's medical friends are a little hazy about this condition, and about fluoridation generally; fluorosis is a rarity, and all of us would have to plead incomplete acquaintance with much of the recent medical literature.

Finally, lest judgment be clouded by charges of "mass-medication" or by dark hints about undiscovered but imminent hazards to health, it is well to reflect that in fluoridation we have a public health measure which has been studied and documented with unusual care and completeness; and that we in Britain have previously hesitated unwisely—for example, in relation to diphtheria immunization.—I am, etc.,

Aberdeen. A. M. THOMSON.

REFERENCES

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Early Diagnosis of Spinal Tumours

SIR,—Drs. H. J. G. Bloom, H. Ellis, and W. B. Jennett (*Journal*, January 1, p. 10) have made a useful contribution to this important condition, which can often be so tragic if the diagnosis is not early. As they clearly indicate, their material is selected, all the cases being Service personnel. Thus the incidence of various tumour types is different to most published figures. They rightly state that this accounts for the absence of meningiomas in their series. But one cannot agree with them that spinal meningiomas are only twice as common in women as men—they quote Learmonth.[1] Elsberg[2] pointed out that nearly all spinal meningiomas occur in women, and in my series[3] of 59 cases 85% were in women and over 90% were seen in patients over 35 years of age.

They give little credit to the part played by radiology in the diagnosis of spinal tumours. While they say that the plain *x* rays of 44% of their cases showed appearances suggestive of spinal tumour, they make no mention of the fact that a *specific* diagnosis can often be made. This applies particularly to neurofibromas, the most important spinal tumours (apart from meningiomas), in that removal so often effects a complete cure. In my series of 53 spinal neurofibromas, no less than 45% showed plain *x*-ray changes enabling a specific diagnosis to be made. The most important sign is, of course, widening of the exit foramen. Bloom, Ellis, and Jennett had 15 neurofibromas, of which 7 are listed as having plain *x*-ray changes (47%). This correlates well with my figures, but the important point is that a specific diagnosis of neurofibroma can so often be made. The significance of normal plain *x* rays in a case of spinal neurofibroma is readily appreciated by considering the anatomical conditions. If the tumour has not invaded the exit foramen and is therefore probably entirely intradural, then the plain *x* rays are likely to be negative, since the tumour normally produces signs of cord compression before it is large enough to splay the pedicles. The differentiation from meningioma can then only be made statistically by considering the age and sex of the patient, although a very high C.S.F. protein will favour neurofibroma.

Again, myelography gets little credit. They say, "Although myelography is by no means always necessary for the detection of a spinal tumour, it is invaluable in accurate localization, and may be the only way in which a neoplasm can be excluded in suspicious cases. . . . The myelogram may also suggest whether the neoplasm is intramedullary or extramedullary. . . ." No one will disagree with these remarks, but what an understatement. One should be able to differentiate extramedullary-intradural lesions from those which are extradural. Such differentiation often takes one much nearer to the pathological diagnosis. Furthermore, the surgeon wants to know the relation of an intradural-extramedullary tumour to the cord—right or left, behind or in front, the last situation being the most unpleasant. Four angiomas are included in the series. How were they diagnosed? Myelography is the only certain method short of surgery or necropsy. The myelographic picture is absolutely characteristic, and should save the patient an operation which never causes improvement and sometimes initiates deterioration.—I am, etc.,

London, W.1. J. W. D. BULL.

REFERENCES

1 *Brit. J. Surg.*, 1927, **14**, 397.
2 *Bull. neurol. Inst. N.Y.*, 1934, **3**, 124.
3 *Acta radiol. (Stockh.)*, 1953, **40**, 283.

Tuberculous Patients in General Hospitals

SIR,—Dr. Peter Stradling (*Journal*, December 18, 1954, p. 1483) has completely "missed the boat" about my whole letter (*Journal*, November 20, 1954, p. 1227). He overlooks the elementary principle that, generally speaking, before any campaign is carried out it is invariably preceded by intensive detailed and careful planning. He also wants to know "where is the money to build such sanatoria?" The answer is simple—from the very same sources which have unlimited supplies of money for war and the fearful destruction and devastation that accompanies it. It is amazing when it comes to the health and well-being of the nation how every obstacle is put in its way.

If Dr. J. Robertson Sinton (*Journal*, December 11, 1954, p. 1418) had read my letter carefully he would have appreciated that, because of my sincere and earnest desire that human beings should be treated like human beings and not like cattle, I want fully equipped sanatoria to be built throughout the country. Complacency and lack of enthusiasm have no place in dealing with such a serious malady. It has been proved in the Scandinavian countries that where there is adequate sanatorium accommodation and mass immunization with B.C.G. the number of tuberculosis patients has been greatly reduced. In my opinion, this is an example which Great Britain might well follow.

In answer to Dr. R. Lester Black, we must take a long-term policy in so far as the tuberculosis patient is concerned, and face up to the realization that, despite chemotherapy, etc., and provision of a couple of wards in general hospitals, the actual number of notified tuberculosis patients has in point of fact increased. In my view the dominant criterion of tuberculosis is not the death rate but the numbers of tuberculosis patients. In any case, as general practitioners know only too well, is not there a big enough waiting-list in general hospitals without taking away a further two wards?

May I conclude by saying that tuberculosis is a subject in which there has always been ample room for argument, but one fact is beyond dispute: without the tubercle bacillus there is no tuberculosis, and for medical men to have the temerity to state that the way things are at present there is no real danger of infection to the nursing staff, etc., through constant contact with tuberculosis patients is fanciful rather than factual. If I have set some of my professional colleagues thinking, then that could be the first real step in Britain's resurgence on the whole question of tuberculosis.—I am, etc.,

Glasgow, S.W.3. ARNOLD B. COWAN.

Negative Tuberculin Test and Positive X-ray

SIR,—In 1949 all schoolchildren in Lewis were tuberculin tested and non-reactors had B.C.G. (if desired). A very high positivity rate was found. The local chest physician kindly *x*-rayed several hundred reactors and reported on them, and in many instances there was radiological evidence of definite intra-thoracic tuberculosis and bed rest was ordered.

A re-survey of all schoolchildren in 1954 yielded some interesting information: (1) A very considerable proportion of those showing radiological signs were now non-reactors. Had all positive reactors been *x*-rayed more such

evidence of reversal might have been available. Some scholars were followed from a decided positive reaction through diminishing sensitivity to negative and then B.C.G. vaccinated. (2) In a few instances (more might have been revealed if all had been *x*-rayed) it has been discovered that children who had had B.C.G. vaccination in 1950 had actually suffered from tuberculous lesions before vaccination. This naturally follows on point 1 if B.C.G. is administered automatically to non-reactors to tuberculin. (3) Consequent upon findings 1 and 2 it seems essential to *x*-ray all children—non-reactors as well as reactors—so that, in the event of a non-reactor having B.C.G. vaccination carried out and later developing intra-thoracic tuberculosis, one will be able to say whether the disease has started for the first time or is the result of a breakdown of a previous lesion. Only in this way will it be possible to evaluate B.C.G. as a preventive measure. (4) Following B.C.G. vaccination the local vaccination reaction and the subsequent allergic reaction vary from person to person. This variation has been considered as due to differences in the technique—even in the case of the same vaccination. It seems to me that an explanation of these variations might be found in points 1 and 2. For example, if a child has at some time had a primary lesion visible on *x*-ray and yielding a positive Mantoux, but in the course of a year or two the allergy but not the *x*-ray evidence disappears and B.C.G. is administered, will the local reaction and subsequent allergic reaction not be more marked than they would have been had infection never been experienced?

X-ray facilities are necessary to enable more investigation to be carried out.—I am, etc.,

Stornoway. R. STEVENSON DOIG.

Trichomonal Vaginitis

SIR,—When Drs. S. R. M. Bushby, R. D. Catterall, and Mary Williamson (*Journal*, January 8, p. 78) found that a new drug, amido-nitrothiazole, exerted a killing power over *T. vaginalis* a hundred times greater than that of acetarsol I am sure that they believed—and naturally—that they might at last have discovered a permanent cure for this harassing disease. But, most disappointingly, they found that nitrothiazole was no more effective in preventing relapse than acetarsol. The large number of drugs which have been used for the treatment of trichomonal infestation of the vagina is evidence of a clinical defeat which is due to causes other than the failure of a specific drug. The cure of vaginitis will not arrive by the discovery of any new drug, however lethal to trichomonas.

All of the many drugs I have used, except absolute alcohol, will eradicate the organism for a few days, as judged by vaginal smear examination and usually the complete disappearance of vulval pain and pruritus. The immediate lethal power of the drugs in ordinary use is sufficient; the real problem is to prevent relapse. The causes of relapse are that the vagina has not been completely disinfested, by failure to pack the whole of the vault around the cervix with the pessaries, or that the organism hides away in the urethral and Bartholin's glands or in the vaginal epithelium. Re-infestation after treatment may also be by coitus, but most improbably due to lavatory seats, as the trichomonas dies by drying, and, though females of all ages use lavatory seats, infestation is rare in children, virgins, and after the menopause. The search for yet more lethal drugs presupposes that *T. vaginalis* is the actual cause of vaginitis, but of this there must be some doubt. For example, it is often found in a normal vaginal smear, while, on the other hand, a smear taken from a severe case may show only an occasional organism or even none at all. The intensity of the inflammatory reaction of the vaginal mucosa is by no means always related to the number of trichomonads found in the smear.

We already have all the anti-trichomonal drugs we need. The essential is the correct application of the one we choose. Self-treatment is entirely useless, for no woman can place pessaries so as to pack the fornices. They must be placed visually through a speculum, under anaesthesia if the vulva is too tender for the passage of a speculum, and kept in place by a light pack of gauze which may be pulled out in twenty-four hours. If the present attack is a relapse the treatment should be repeated during the last days of menstruation for at least three months. Meanwhile the patient should remain celibate. Despite, however, the most careful and thorough treatment a few women will relapse at intervals, perhaps for years. Trichomonas is not the whole answer to the problem of vaginitis. It may be caused by associated bacteria or even a virus.—I am, etc.,

London, W.1. ALECK BOURNE.

Mepacrine and Malaria in Children

SIR,—Dr. S. B. Dimson in his paper, "Congenital Malaria in England" (*Journal*, November 6, 1954, p. 1083), mentions the toxic effects of intramuscular injections of mepacrine reported by me[1] in small children in a paper published four years ago. Your readers might be interested in another, more recent case of immediate effects and serious sequelae of an intramuscular administration of mepacrine to an infant.

A well-developed European baby, 6 months of age, on suppressive quinine regimen from birth, had an onset of fever without any obvious clinical symptoms. In spite of repeatedly negative blood examinations for malaria parasites the infant was given an intramuscular injection of 50 mg. of mepacrine musonate. Within 20 minutes after the injection it stiffened, started rolling its eyes, lost consciousness, developed tonic and clonic convulsions, became deeply cyanosed, and collapsed. It was given nikethamide, artificial respiration, and was rushed to the hospital, where it received a large dose of chloral, oxygen, and cardiac stimulants. A lumbar puncture showed the cerebrospinal fluid under slightly increased pressure but otherwise normal. The temperature rose to 104° F. (40° C.). As the clonic convulsions kept reappearing the child was kept on chloral and oxygen for several days. Under this treatment and with excellent nursing the temperature slowly decreased, the convulsive status abated within a week, but occasional twitchings of arms and legs were still present and there were bouts of general muscular rigidity. The skin was yellow and mepacrine was excreted in urine for several days.

On discharge from the hospital the child showed an impairment of head control, hypotonia of the trunk and of one arm. Two months later the child received a good deal of expert attention at one of the London hospitals, where no major abnormality was found, apart from poor head control, failure to make any attempt to sit, and a feeble grasp. The cerebrospinal fluid showed a slightly raised protein content. To-day, after nearly a year, the child shows an improvement of the tonus of its neck muscles, but it has a partial paralysis of one arm, shows now symptoms of spastic paraplegia of legs, and appears to have a retarded mental development.

Admittedly, cases of such severe encephalopathy due to mepacrine are uncommon, but it seems that they could be avoided by more critical intramuscular administration of this drug to infants and small children or, at any rate, by the use of chloroquine, which, apart from being an excellent antimalarial, is also much better tolerated by all age groups.—I am, etc.,

Yaba-Lagos, Nigeria. LEONARD J. BRUCE-CHWATT.

REFERENCE

[1] *British Medical Journal*, 1950, 2, 7.

Encephalitis after Yellow Fever Vaccination

SIR,—The *Journal* of November 20, 1954, has just reached me, and I was interested to read Dr. Leonard Roodyn's letter (p. 1226) on encephalitis following yellow fever vaccination. I am prompted to write to you, as I have just had under my care an infant suffering from this condition; this is the fourth to be reported in recent weeks. A male child, aged 3 months, was vaccinated in the United Kingdom against smallpox on October 30 and against yellow fever on November 22. The parents arrived at Kano by air on November 30. On December 3 the child was admitted to hospital, as he would not take his feeds. On December 4

the rectal temperature was 103° F. (39.5° C.). He developed a Jacksonian attack involving the left limbs; this was accompanied by a left facial palsy and deviation of the eyes to the left. Direct questioning of the mother produced the story given above. The information about the yellow fever vaccination had not been given previously, as, quite naturally, the parents had not realized the significance of this point. The child did well and now appears to be normal.

From the experience of this case, and that recorded by Dr. L. G. Scott (*Journal*, November 6, 1954, p. 1108), it would appear that cases of encephalitis following yellow fever inoculation may occur when recently vaccinated children are many hundreds of miles from the centre where the inoculations were given. In this way hospitals in the United Kingdom may not be aware of the accident even if the correct diagnosis is made. Parents who travel with young children should be advised not to leave the United Kingdom for at least three weeks after receiving yellow fever vaccination in case encephalitis should follow, although this must be an infrequent complication.

With regard to the vaccination of young babies who travel from an endemic area to the United Kingdom, without stopping in a receptive area, it might be advisable to recommend that vaccination against yellow fever is withheld, as injections in these cases are given not so much to protect the individual as to prevent the spread of yellow fever in Britain, a possibility so remote that it can be ignored.—I am, etc.,

Kano, Nigeria. E. A. BEET.

Tests of Hearing

SIR,—While agreeing with most of the remarks made by Professor A. W. G. Ewing in his statement on sweep frequency-screening tests of hearing (*Journal*, January 1, p. 41), it would appear desirable to point out that partial deafness of the severity necessitating special educational treatment should be detected before the age of 5 years if it is of congenital origin. Such deafness should be detected preferably before the age of 1 to 2 years so that the child may receive auditory training during the period of normal physiological speech development. If acquired deafness should occur, rehabilitation should start straight away, as soon as the child is well enough. It would be unfortunate if the impression were given that it is satisfactory to defer tests of hearing until the routine group tests are done at the age of 5. The search for deafness at an earlier age is long overdue. The post-natal clinic would seem an ideal place for increasing the mother's awareness of the possibility and implications of partial deafness.—I am, etc.,

London, W.1. EDITH WHETNALL.

Medical Aspects of Amateur Boxing

SIR,—I was interested to read the article on amateur boxing by Drs. J. L. Blonstein and Edwin Clarke (*Journal*, December 25, 1954, p. 1523). As medical officer I attend weekly tournaments of one of the premier amateur boxing clubs in Glasgow. I must have attended over 200 tournaments and seen over 2,000 bouts. I disagree with the conclusion of the article in question. Far from being a useful and justifiable *sport*, amateur boxing is a dangerous, and often brutal, happening. Firearms, swords, daggers, razors, broken bottles, and coshes produce appalling injuries—I would say that boxing comes next on the danger list. Perhaps all-in wrestling is a "wee shade" more dangerous. Virtually, each boxer steps into the ring with the intention of injuring his opponent, especially his opponent's cranium and its contents.

Concussion produces an oedema of the brain, and this pathological condition does not clear up quickly. Though a boxer regains consciousness by the count of ten, is able to bathe, dress himself, and have a light meal, he is not recovered. I have known of a young man being off work for many months following a knock-out (by concussion). Much is made of medical control in the article. No such control exists here. Recently a boxer was knocked out on a Saturday and again on the following Monday. Boxers here are examined before a contest only if it is an international or a championship match. The only difference between professional and amateur boxing, from my point of view, is the distance of rounds. I know of two severe eye injuries, one, at least, involving the retina. I note that the London article makes no mention of solar plexus blows, the effects of which are very distressing not only to the recipient but also to the spectators, and, not least, to the medical officer.

As a nation, are we in a position to afford this type of disability production? I admit that, after many years, "boxing" grows upon one—an innate sadistic admiration for "guts."—I am, etc.,

Newton Mearns. JAS. C. LAURIE.

Cardiac Asthma

SIR,—Although rare, acute pulmonary oedema is probably one of the most alarming emergencies encountered in general practice. As Dr. J. G. M. Hamilton (*Journal*, January 1, p. 39) says, morphine is an effective drug for the relief of such attacks, but it is not without potential danger, particularly when administered intravenously. In a condition in which there is already extreme respiratory embarrassment, the depressant action of morphine upon the respiratory centre should be avoided if there is an alternative drug which can be used. Dr. Hamilton explains the effect of morphine by a multiplicity of actions, most of which could be achieved with alternative hypnotic and analgesic drugs. But, in fact, such other drugs are ineffective.

I believe that morphine relieves this condition by virtue of its peripheral vasodilator action. Its effect is therefore analogous to that of tolazoline[1] and other vasodilator drugs,[2] but these have the advantage of creating no respiratory depression. In hypertensive left ventricular failure, peripheral vasoconstriction is the precipitating factor in initiating and maintaining the attack of acute pulmonary oedema. My most recent case was a woman of 63 with a basal hypertension in the region of 220/120. She suffered an extremely severe attack of acute pulmonary oedema in the night and, when I reached her, was extremely distressed and practically unconscious. The blood pressure had risen to 285/150 and she exhibited the usual signs of intense peripheral vasoconstriction. Tolazoline hydrochloride, 25 mg., was injected intravenously, and one minute later the blood pressure had fallen to 225/100, with subsequent resolution of the attack. The use of vasodilator drugs carries with it none of the dangers of hypotensive agents, such as the methonium compounds, for the production of peripheral vasodilatation merely returns the blood pressure to its previous basal value and there is no danger of irreversible hypotension. In mitral stenosis and type II nephritis, a similar mechanism may play a part in producing attacks of acute pulmonary oedema, for I have relieved such attacks in these two conditions with vasodilator drugs and observed similar blood pressure changes. On the other hand, in myocardial infarction the use of any drug which lowers blood pressure may be an extremely hazardous procedure.

The general practitioner has a unique opportunity for studying and treating this condition. By the time the patient reaches hospital the attack may be in its later stages, and often subsiding, or the patient may be dead. In the prevention of subsequent attacks in hypertensive cases, I think more can be done than was suggested in Dr. Hamilton's article. I doubt whether general practitioners will be content to sit back and watch their patients leading a "digitalis life," with all its accoutrements of semi-invalidism, when more active measures are available. Surely it is preferable to reduce the patients' blood pressure, with consequent decrease in cardiac enlargement and prevention of further acute episodes of failure.[3]

It is usually possible to control most cases of hypertension with a combination of hypotensive agents, the composition of which may have to be varied from case to case. Probably the most useful combination in general practice is reserpine with hexamethonium or pentolinium by mouth. Thus in the case already quoted there were three severe episodes of acute pulmonary oedema in the first fortnight, before the blood pressure was controlled with these two drugs. In the following four months the blood pressure has been kept in the region of 150/100, a lower value than this producing postural faintness, and there have been no further attacks of left ventricular failure. It might be argued that

such treatment does not maintain a low blood pressure value and that hypertensive peaks occur as the effect of each dose wears off. Whether this is so or not, the clinical improvement in this case is striking and is associated with almost complete reversal of the cardiographic appearances of left ventricular strain and diminution in heart size on *x* ray. I have observed similar effects in a number of other cases of hypertension treated in like manner. I believe that it used to be said that once a patient suffered more than one attack of acute pulmonary oedema the prognosis was poor. With our present therapeutic armamentarium, there is no longer any need for such a pessimistic outlook.—I am, etc.,

Twickenham, Middx. DAVID WHEATLEY.

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[1] Wheatley, D. (1952). *British Medical Journal*, **1**, 1174.
[2] —— (1954). *Proc. roy. Soc. Med.*, **47**, 327.
[3] Smirk, F. H., *et al.* (1954). *Lancet*, **2**, 159.

SIR,—In his excellent refresher course on "Cardiac Asthma" (*Journal*, January 1, p. 39) Dr. J. G. M. Hamilton points out that rapid venesection *may* be usefully employed. In 1924 I published a paper[1] in which I showed that a significant hydraemia occurred in such a patient in a few hours after a venesection (300 ml.), and I have since successfully treated many cases of acute pulmonary oedema and of chronic stasis of the lungs with venesection and, of course, with morphine in the acute stage. I consider venesection (300 ml. is sufficient) as the treatment of choice in these cases. I quite agree with Dr. Hamilton on the long-term management of these cases.—I am, etc.,

Aalborg, Denmark. CARL SCHWENSEN.

REFERENCE

[1] *Ugeskr. Læg.*, 1924, **86**, 289.

Dyspareunia

SIR,—I was interested to read in Mr. R. Christie-Brown's letter (*Journal*, January 8, p. 106) of the existence of a clinic for the exclusive purpose of treating dyspareunia. I wonder if it is generally realized that this complaint is often due to pathological processes in the urethra—sometimes resulting in vegetations. Whatever the changes, they are readily detected by urethroscopy and are generally amenable to the appropriate treatment. I have had a number of such cases where fertility has replaced infertility.—I am, etc.,

London, W.1. H. P. WINSBURY-WHITE.

SIR,—I was interested to read that my friend Mr. Christie Brown (*Journal*, January 8, p. 106) "has become increasingly aware of the large part which dyspareunia plays" in the causation of infertility. It is possible that he will find that a high percentage of women attending an ordinary gynaecological out-patient department also suffer from the same troublesome complaint. If he would try cauterizing the internal os uteri with a stick of silver nitrate, I think he would find that he would cure most cases of dyspareunia provoked by deep penetration of the penis and that his new clinic might prove unnecessary.

The same treatment, provided women with gross pelvic pathology were excluded, would also cure most cases of lower sacral backache, frequency and urgency of micturition, stress incontinence of urine, and lower abdominal pain, including right iliac fossa pain, for which so many normal appendices and not a few ovaries are needlessly sacrificed.—I am, etc.,

Bradford. G. W. THEOBALD.

SIR,—I was interested in Mr. R. Christie Brown's letter (*Journal*, January 8, p. 106) drawing attention to the existence of a "dyspareunia clinic." This condition is a sadly neglected complaint and one far more common than is generally realized. I am prepared to accept that many patients seek advice for a variety of symptoms (of which infertility is one) when the basic trouble is their inability to participate in a normal married life, but surely only introital dyspareunia is likely to be associated with infertility as cause and effect. In such cases levator spasm is sufficient to prevent penetration.

I agree that general practitioners cannot be expected to deal with these cases, but I beg to suggest that these patients can often be treated successfully in an out-patient clinic by simple instruction and the use of vaginal dilators. Only the most refractory would I refer for a psychiatrist's assistance.

These cases are a challenge to the patience and ingenuity of the non-surgical aspect of our specialty. Is there not too much tendency nowadays to split up gynaecology into various component clinics: contraception, infertility, hormone, and now dyspareunia?—I am, etc.,

Cambridge. OSWALD LLOYD.

Changes in the Mental Health Services

SIR,—In reply to Sir David Henderson (*Journal*, January 8, p. 104), I must apologize for my injustice to Scotland (*Journal*, December 18, 1954, p. 1484). I wrote with first-hand knowledge of Edinburgh only, and made the unwarranted assumption that the conditions obtaining here were those of the Scottish mental health service as a whole. I am well aware of the existence of Jordanburn Hospital and the nursing-homes, which I visit frequently, but these establishments have nothing to offer the type of patient under discussion. If a patient is so disturbed by his illness that he refuses to accept treatment, his admission to these places cannot be effected. If he accepts the need for treatment, then he can equally well go as a voluntary patient to a mental hospital, though the nursing-homes have the merit of being without the mental hospital.

I am also aware of the existence of an observation ward at the Royal Infirmary of Edinburgh, but am equally aware of the categories of patients who may be admitted there. They are (1) disturbed patients in other wards of the Infirmary, (2) patients from corrective establishments, and (3) cases of attempted suicide. They do not admit acute psychoses from the Edinburgh area in general. These facts I have confirmed from the Superintendent's office before writing. Despite, therefore, the sympathetic attitude of the Board of Control for Scotland in 1906, the facts in Edinburgh in 1955 are that there is no alternative but to certify an acutely disturbed patient who declines to go willingly to a suitable establishment.—I am, etc.,

Edinburgh, 5. JOHN MARSHALL.

Crying in Infants and Children

SIR,—It was with great interest that I read the article by Professor R. S. Illingworth on infant crying (*Journal*, January 8, p. 75). In a hospital for mental defectives in this town it is noticeable that genuine crying with tear formation is extremely rare among the low-grade patients. Crying is more common among the females than the males, and among the females it is much more common in the higher-grade than in the lower-grade patients.

It would be instructive to learn why crying should cease while other childish behaviour patterns, thumb sucking, rocking, and head banging remain. Perhaps there is some explanation depending upon maturation of the central nervous system.—I am, etc.,

Chipping Norton. F. E. JAMES.

SIR,—Professor R. S. Illingworth, in his article on "Crying in Infants and Children" (*Journal*, January 8, p. 75), refers to the obscurity of the mechanism of vomiting in small children who have been crying more than a quarter to half an hour. May I mention the following observation which may throw light on this mechanism?

On reviewing some discarded chest radiographs of young children and infants, there were a few radiographs where the lung fields were almost completely obscured by an opacity continuous with the heart and mediastinal shadow. I was informed (and it is probably common knowledge to our

x-ray colleagues) that it frequently happened that in a crying young subject (and it need not be vociferous crying) such radiographs were obtained; pacification allowed unobscured radiographic views of the lung fields. If every case of crying is indeed accompanied by this hyperaemia, and if it is maintained for long periods, then it may lead to mucus exudation in unusual amount from the bronchial epithelium which would gather in the bronchial lumen. Such mucus stimulating the oropharynx leads to reflex vomiting (in severe pneumonias in children and whooping-cough, cough followed or accompanied by vomiting is a frequent occurrence). A subsidiary factor may be stimulation of the medullary vomiting centre by hypoxia of the blood in the cerebral blood vessels resulting from pulmonary-bed pooling.—I am, etc.,

Romford, Essex. B. SKLAN.

Obstruction from Orange Pith

SIR,—May I add a further case of acute intestinal obstruction caused by swallowing an unmasticated piece of orange (*Journal*, December 18, 1954 p. 1484)?

A man aged about 45 years was seen by me in the casualty department complaining of colicky abdominal pain and vomiting for a duration of six hours. This was on a Sunday during the football season. Examination revealed this to be an early case of small bowel obstruction. The patient had a polya type of partial gastrectomy performed at the same hospital five years previously. A provisional diagnosis of obstruction due to post-operative adhesions was made. Laparotomy revealed small bowel obstruction caused by a foreign body impacted in the lumen of the gut two feet proximal to the ileo-caecal valve. Removal of the foreign body relieved the obstruction. Examination revealed it to be an intact unmasticated "quarter" of a fair-sized orange. On taxing the patient's memory the following day, he recalled having a similar piece of orange in his mouth at a most inopportune moment during the course of a football match on Saturday. During the excitement that followed a victorious goal the orange had disappeared from mouth and mind.

Looking back on the case, I do not believe that such a large bolus could have gone through a normal pylorus. That this is one of the lesser known hazards of gastrectomy should be borne in mind. Whether it can be classed as one of the hazards of football, I shall leave to your readers' imagination.

I wish to thank Mr. R. Cunliffe-Shaw for allowing me to mention this case.—I am, etc.,

London, S.W.1. N. H. ANTIA.

What is Health?

SIR,—I have read with great interest the report of the Kent Paediatric Society[1] and your annotation (*Journal*, December 11, 1954, p. 1409) under the above heading. A similar study of an older age group composed of university students has been carried out over the last eight years in the University of Aberdeen, where the approach to the problem has been different in many respects, chiefly in regard to the assessment of health. Following initial trials no effort is now made in this department to assess health on a mathematical basis. I would hesitate to accept a series of physical and intellectual scores as providing accurate measurement. Some of the conditions on the Society's marking form do not seem to me to warrant degrading, and I do not think it is yet clear as to what extent intelligence and the possession of personality assist the individual to adapt harmoniously either within himself or in relation to things without, which is what fundamentally constitutes health. It may be that an intelligent, highly reactive personality does not adapt so harmoniously to environmental agents as a more placid individual.

The procedure here is as follows: Each student coming for first examination has a careful interview of about an hour's duration followed by a physical examination. On completion the individual is placed, on a purely arbitrary assessment, into one of four categories. The first is composed of those whose all-round qualities are outstanding, the third of those who are quite obviously unfit, whilst in between is placed the largest section, constituting the average. The latter is again divided into high and low, so that the groups are labelled 1, 2a, 2b, and 3 respectively. The student's progress at University is followed up, and each receives at least one re-examination, whilst those who stay over three years receive two or more reassessments. By means of a punch file record system the factors concerned with each group can be correlated. It is realized that assessments of this nature can only be of value if carried out in respect of adequate numbers and over sufficient length of time. A ten-year survey is in progress and it is hoped to publish the results in another two years.

This method of approach obviously lacks the precision of a more exact numerical measurement, but it is felt that to attempt to apply scientific accuracy to so ill-defined a subject as health may result in a less accurate impression than a more arbitrary assessment of what we all understand and appreciate, but which we find so difficult to define and measure. In spite of any criticism which these remarks may seem to convey I would like to congratulate the Kent Paediatric Society on its very fine pioneer survey.—I am, etc.,

Aberdeen. A. H. MACKLIN.

REFERENCE

[1] *A Study in the Epidemiology of Health*, published from the Health Department, 14, Brampton Road, Bexleyheath, Kent.

Sudden Death in Labour

SIR,—From the incomplete evidence submitted it would seem that the death reported by Dr. Patricia E. Campbell (*Journal*, January 8, p. 87) was probably due to massive amniotic emboli due to uterine contractions, and not to the penicillin administered over an hour before.—I am, etc.,

Oxford. JOHN STALLWORTHY.

SIR,—I have read with interest Dr. Patricia E. Campbell's stimulating report of sudden death in labour following injection of penicillin (*Journal*, January 8, p. 87). Ascribing such a major catastrophe, however, to a penicillin injection, without any apparent proof, cannot be accepted easily, and with apologies to Dr. Campbell I feel obliged in the interests of obstetrics to criticize the diagnosis. Is it not rather untenable that hypersensitivity to penicillin should express itself in such manner and degree one hour and a quarter after injection without any prior warning or reaction? This would not be in keeping with the patterns of drug sensitivity.

The unexpected onset in normal labour of vomiting, cyanosis, and sudden death with the morbid findings of pulmonary petechiae and incoagulable blood primarily suggests a diagnosis of liquor amnii embolism and a further definitive search for evidence of extrauterine amniotic content is then warranted. It is only 14 years since Steiner and Lushbaugh[1] first brought this pathological entity to our notice, and to date there are only about 50 cases on record. It is not surprising then that many as yet are unaware of the condition. In the reported case of Dr. Campbell's it is not stated whether there was a histological search for epithelial squames in the lung and, in their absence, if any special staining was used to outrule the presence of liquor amnii fat in the pulmonary blood vessels or whether there was any rent or tear in the amnion explaining the mode of occurrence of embolism.

"Obstetric shock," one time accepted as idiopathic in nature, has more recently become clearer in its aetiology, mainly through a more comprehensive approach to morbid anatomy. In such unknown estate no doubt drug anaphylaxis is entitled to a dwelling, but in Dr. Campbell's case I feel that another housing applicant should primarily be proved less deserving.—I am, etc.,

Galway. DONAL O'SULLIVAN.

REFERENCE

[1] *J. Amer. med. Ass.*, 1941, **117**, 1245.

SIR,—I was interested to read the report by Dr. Patricia E. Campbell of a case of sudden death in labour following a penicillin injection (*Journal*, January 8, p. 87). There are several features about it, however, which make the diagnosis of anaphylaxis seem unsatisfactory.

These are as follows : (1) The time interval of one hour between the injection and collapse of the patient is rather long for intravenous injection of the drug—probably the cause of the majority of sudden deaths after penicillin injection—to have been responsible. (2) Reporting the use of massive doses of penicillin, McLean[1] records sudden death of three patients, and says, "As death occurred in all cases within twelve hours of the initial dose, it seems unlikely that anaphylaxis was responsible." (3) The case clinically appears to present all the features of amniotic fluid embolism described originally by Steiner and Lushbaugh,[2] and subsequently by Reid *et al.*,[3] in the United States of America, and by Shotton and Taylor[4] in this country, and the necropsy findings are not inconsistent with this condition. Dr. Campbell does not state whether or not the lungs were examined histologically.—I am, etc.,

Glasgow, S.1. GORDON BRILL.

REFERENCES

1 *Practitioner*, 1955, **174**, 45.
2 *J. Amer. med. Ass.*, 1941, **117**, 1245.
3 *Amer. J. Obstet. Gynec.*, 1953, **66**, 465.
4 *J. Obstet. Gynaec. Brit. Emp.*, 1949, **56**, 46.

Appendicectomy in Chronic Appendicitis

SIR,—In common no doubt with the majority of your readers, I have been very interested in the correspondence on appendicectomy for "chronic" appendicitis which followed the publication of the paper by Messrs. I. McLennan and J. K. Watt (*Journal*, September 25, 1954, p. 736). I was particularly impressed by the letter from Professor J. Chassar Moir (*Journal*, December 11, p. 1415) in which he pointed out the fact—shown in their paper—that "chronic" appendicitis appears to be much commoner in females of menstrual age and that, in his opinion, this is usually attributable to disordered ovarian function.

I am in the process of preparing a paper which lends much support to this hypothesis. In an analysis of all cases with pain in the right iliac fossa, as the presenting symptom seen at one particular surgical out-patient clinic at a provincial teaching hospital during the course of 12 months, the following figures were obtained : females 52 ; males 11 ; total 63. Thirty-seven of the females were between 14 and 30 years of age, the majority being either in the late 'teens or early twenties. These girls were nearly always complaining of intermittent "stabbing" or "niggling" pain in the right iliac fossa (and frequently in the left iliac fossa if specifically asked) which usually lasted anything from a few minutes to several hours, with little or no constitutional upset and usually no abnormal physical signs at the time of examination, although deep tenderness in the right iliac fossa had often been found by their own doctors during or shortly after an attack. In 33 out of the 52 females a diagnosis of ovulation pain was made and the patient reassured. Of the remaining 19 females, of whom the majority were between 40 and 50, one had acute appendicitis and three were thought to be recovering from a recent acute attack, whilst in the remainder a variety of disorders was found, including constipation, renal, gall-bladder, and frank gynaecological disease, plus one pregnancy. Among the 11 males, 6 had a history and/or signs consistent with recent acute or recurrent appendicitis, whilst two were found to be suffering from severe constipation. A right basal lung cyst, a large para-umbilical hernia, and right myofascial lumbar strain completed the list of males. During the same 12 months, 10 females between the ages of 15 and 30 were operated on for "apoplectic" ovary (ruptured lutein cyst) and 8 treated conservatively in the beds of this unit. It is believed that this condition, particularly in a minor form, is by far the commonest cause of recurrent pain in the right iliac fossa in young women.

Appendicular colic, characterized by recurrent central abdominal pain generally lasting only a few minutes at a time and often associated with slight deep tenderness over the appendix but without local rigidity, is a much more plausible explanation for the symptoms relieved by appendicectomy particularly in childhood. In such cases, the appendix is nearly always normal to the eye of the surgeon and to the unbiased pathologist. It may be kinked and usually contains inspissated faecal matter, but it is rarely chronically inflamed. In so far as constipation appears to be the basic cause of appendicular colic, the condition tends to cure itself in time, but this may extend over many years. For such cases, appendicectomy is probably a justifiable but certainly not an essential procedure. While chronic appendicitis undoubtedly exists as a pathological entity, and probably as the sequel to acute or recurrent attacks, it is, I think, a comparative rarity, if for no better reason than the vigilance of the average G.P. in referring all suspicious cases of acute or subacute appendicitis to hospital for emergency admission. Clinically, chronic appendicitis is either silent or declares itself only during acute exacerbations. Following the resolution of an appendix abscess, the appendix is histologically chronically inflamed, yet the patient is symptom free unless there is a recurrence of acute inflammation.

My conclusions, for what they are worth, are: (1) Chronic appendicitis is relatively rare and is a sequel to acute inflammation. (2) Chronic appendicitis *per se* is symptomless. (3) Appendicular colic is common, particularly in children, and is due to inspissation of faecal matter in perhaps a kinked but not usually a chronically inflamed organ. (4) Appendicular colic can be produced only if the wall of the appendix is capable of actively contracting, and this function is inevitably inhibited by fibrosis. (5) Acute-on-chronic (or recurrent) appendicitis is characterized more by persistent pain in the right iliac fossa (lasting continuously for several hours or days) and less by initial central colic. (6) Recurrent attacks of pain localized to the right iliac fossa and lasting only short periods (minutes to perhaps an hour) are rarely due to appendicitis. (7) Recurrent niggling pain in the right iliac fossa of young women is generally due to disordered ovarian function.—I am, etc.,

London, W.C.1. A. HENRY MILLARD.

Distribution of R.M.B.F. Christmas Gifts

SIR,—I am sure that your readers will be pleased to learn that the contributions to provide Christmas gifts for the beneficiaries of the Royal Medical Benevolent Fund amounted to £2,775. We were able to distribute £8 to each of them.

The warmth of gratitude expressed in letters of thanks would have gladdened the hearts of the contributors, and of yourself, Sir, for giving space so generously for the publication of the appeal.—I am, etc.,

WEBB-JOHNSON,
President,
London, S.W.15. Royal Medical Benevolent Fund.

POINTS FROM LETTERS

Fixation of Blood Smears

Mr. N. V. GURJAR (Bombay) writes: I have been using successfully a 7% solution of sulphosalicylic acid as a fixative for blood smears. More than 3,000 smears of blood and marrow have been fixed by this method for a couple of seconds and then stained with different haematological stains. The results have been excellent. The cytological morphology is better as compared with alcohol fixation. Another advantage is that smears so fixed can remain (unstained) for any length of time without any fungus growth, which is a common feature of alcohol fixation. Recently I have also fixed some tissues for histological section with 10% solution of sulphosalicylic acid for 24 hours, and this has shown less shrinkage in cell cytology. This might prove a bit expensive in comparison to formol-saline or Bouin's fixative, but the advantage of getting better morphology could be a consideration particularly when dealing with small biopsies.

The Future of Surgery

Dr. E. F. BLUMBERG (London, S.W.3) writes: With reference to Sir Heneage Ogilvie's statement (*Journal*, December 18, 1954, p. 1435) that "the contributions of Germany to surgical advance in the last 50 years have been pathetic," for the years since 1933 your author is obviously correct. The first 25 years, however, produced a vast number of great names. I am including a small collection—Kocher, Trendelenburg, Lexer, Israel, Enderlen, Czerny, Bier (lumbar anaesthesia), Kehrer, Koerte, Garré, Sauerbruch.

Obituary

R. J. WILLAN, C.B.E., M.V.O., M.S., F.R.C.S.

Professor R. J. Willan, who died in London on January 12 at the age of 77, was for many years an outstanding surgeon in the north of England, and his reputation was high throughout the surgical world. Although a general surgeon, he was particularly well known for his genito-urinary work. He gave devoted service to his hospital, the Royal Victoria Infirmary, Newcastle-upon-Tyne, and to his university; he reached flag rank in the R.N.V.R. and was surgical adviser to the Ministry of Health; and he was a valued counsellor in the affairs of the Royal College of Surgeons of England and of the British Medical Association.

[Dorothy Wilding

Robert Joseph Willan was born on January 10, 1878, the second son of John Willan, J.P., of Durham. From Durham School he went on to the University of Durham, graduating M.B., B.S., with honours, in 1906. He won the Gibb scholarship in pathology in 1904, the Charlton scholarship in the principles and practice of medicine in 1905, and the Stephen Scott scholarship in 1908. Later, in 1920, he was awarded the Heath scholarship, which is awarded, also by Durham University, for an essay or paper based on personal investigations. He took the F.R.C.S. in 1908, and in the following year proceeded to the M.S., with first-class honours. After graduation Willan was house-surgeon and surgical registrar at the Royal Victoria Infirmary and senior house-surgeon at St. Peter's Hospital, London. In 1914 he was elected to the honorary staff of the Royal Victoria Infirmary as assistant surgeon, becoming full surgeon in 1922, and his skill, resolution, and hard work quickly gained him a wide reputation and an extensive practice. In due course he became senior honorary surgeon to the Infirmary, and then consulting surgeon when he retired in 1938, and for some time he was chairman of the honorary medical and surgical staff committee. An appointment of which he was particularly proud was that of honorary life governor of the Infirmary made soon after his retirement. He also served as honorary surgeon to the Ingham Infirmary, South Shields, to the Newcastle-upon-Tyne Dental Hospital, and to the Whickham and District Cottage Hospital. When the late Professor G. Grey Turner came south to become professor of surgery at the British Postgraduate Medical School at Hammersmith in 1935 Willan succeeded him in the chair of surgery in Durham University, a post which he filled with distinction until his retirement in 1942. He was then appointed emeritus professor. He was a past-president of the Durham University Medical Society and of the Newcastle upon Tyne and Northern Counties Medical Society.

At an early stage in his career Willan joined the Volunteers, being attached to the Durham Light Infantry. Later he transferred to the Royal Naval Volunteer Reserve, retiring in 1933 with the rank of surgeon-captain after many years' service. During the first world war he served with the Grand Fleet and was for a time medical adviser to Prince Albert (later King George VI), and he also treated and gained the friendship of Admiral Jellicoe. He was awarded the Volunteer Decoration in 1919; and he was Honorary Surgeon to King George V from 1930 to 1933.

In the second world war he again served the Royal Navy as consultant in surgery for Scotland, with the rank of surgeon rear-admiral, and he was also surgical adviser to No. 1 Region of the Ministry of Health. He was appointed M.V.O. in 1915, O.B.E. in 1919, and C.B.E. in 1946.

From his early days in Newcastle Willan took a great interest in the work of the British Medical Association. Beginning as honorary secretary of the Newcastle-upon-Tyne Division in 1912, he was scientific secretary of the North of England Branch from 1915 to 1922, and his merits in these posts gained him the position of chairman of the Division in 1924–5 and president of the Branch in 1929–30. Much of the success of the Association's Annual Meeting held at Newcastle in 1921 was due to his organizing ability as honorary local secretary of the meeting. He served as a vice-president of the Section of Surgery at the Glasgow Meeting of the B.M.A. in 1922, was a representative to the Centenary Meeting held in London in 1932, and a member of the Council for a year (1931–2). He worked on a number of committees of the Association, and was particularly interested in the Science Committee, of which he was a member for nearly 30 years. He was chairman of its library subcommittee from 1946 until his death and was closely concerned with the move of the library to its present home in the garden-court wing of B.M.A. House.

Willan wrote a large number of articles for the various medical journals, articles chiefly concerned with subjects relating to the genito-urinary organs. All his writings were characterized by sound and practical common sense. In 1939 the seal of their approval was given to Willan by his surgical *confrères* when he was elected to the council of the Royal College of Surgeons of England, and he remained on the council for eight eventful years.

Of medium height and sturdy in build, Willan had the misfortune to lose the sight of one eye through an accident in later life, but he was never heard to complain of this infirmity. Good-natured in temperament, quiet in demeanour, rather reticent in giving his opinion, he could always be relied on to speak to the point. After his retirement from hospital and private practice he moved to London, where he regularly attended the Savoy Chapel, for he was very proud of his Membership of the Royal Victorian Order and he loved the quiet and the atmosphere of that religious oasis. After coming to London Professor Willan interested himself in medical charity. He was a member for some years of the council of Epsom College, where he was for two years chairman of the Special Committee: after that he was chairman of the Conjoint Committee for one year, but in 1954 had to decline nomination for re-election owing to the state of his health. He was also for a few years on the committee of management of the Medical Insurance Agency.

Professor Willan's wife, formerly Miss Dorothy E. Shawyer, died in 1949, after they had been married 39 years. There were one son and two daughters of the marriage.

G. McC. writes: No medical officer who has served on the permanent list of the Royal Naval Volunteer Reserve will have failed to have noted with regret the death of Robert Joseph Willan, for, although he was a surgeon and teacher of repute, it was his connexion with, and career in, the Royal Navy of which he was most ready to talk in his later years. As a very young man he joined the Royal Naval Volunteer Reserve shortly after its foundation. Serving in the years immediately prior to the first world war, he took an active part in training and preparing the Tyne Division for the part this Division was to take and for which he himself was mobilized in August, 1914. During his four and a half years of active service he wrote what became a minor classical publication entitled, *Clinical Notes for Surgeon Probationers*, which became the medical Bible for all those unqualified medical students who had medical charge of destroyers and other small ships. His place as a member of the R.N.V.R. in the Royal Navy became established when, as surgeon in the Hospital Ship *Plessey*, he was called upon to operate, in an emergency, on the Duke of York, who was later to become King George VI.

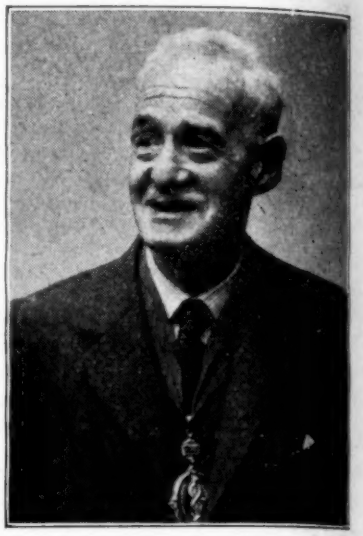
After the war he continued as a senior medical officer, attaining the maximum rank allowed in the Reserve, of surgeon captain, and in that rank holding the position of King's Honorary Surgeon. Retiring on the age limit in 1935, he kept close touch with his old Division and with Naval medical thought, and in 1939, on the outbreak of the last war, it was a great grief to him that he was considered too old to serve. Later he was re-employed as a surgeon captain (retd.), R.N.V.R., and was finally promoted to the rank of acting surgeon rear-admiral, R.N., which was a source of pride to himself and of satisfaction to those who knew him and had worked with him, and was interpreted as a tribute to the permanent Royal Naval Volunteer Reserve Medical Branch. After the war he kept up his connexion with the Tyne Division, and liked nothing better than to come North from his retirement to talk over old times with other "old salts."

J. B. MILLER, M.D., LL.D., D.P.H.

Dr. J. B. Miller, of Bishopbriggs, whose death at home on January 14 we record with deep regret, was chairman of the Representative Body from 1946 to 1948, and one of the most popular and respected figures for many years in the central affairs of the British Medical Association. He seasoned its assemblies with his humour and wit, but behind the drollery was a keen intellect, practical wisdom, and a notable capacity for friendship. He was 77 at the time of his death.

In the Association, after filling many positions in Scotland, including the chairmanship of the Scottish Committee, and also undertaking much useful work at the London headquarters, Dr. Miller was unanimously called to the chairmanship of the Representative Body, the first Scottish practitioner to hold that office. It is an office which demands, not so much skill in the shaping of policy or the conduct of negotiations, as exceptional qualities of chairmanship—firmness, impartiality, politeness; the ability to prick a pretentious bubble, to relieve a strained situation, to rebuke the rude or restive and prod the bored or indifferent; and a detailed knowledge of the business of the meeting. Miller's personality was such that he could display all these qualities and capacities during his three years of chairmanship, among the most difficult years the Representative Body has ever passed through.

James Blakely Miller was born on April 9, 1877, at Kirkintilloch in Dunbartonshire, the son of the Rev. Andrew Miller. He was educated at Glasgow High School and at the University, where he became secretary of the Medico-Chirurgical Society. After graduating M.B., Ch.B. (with commendation) in 1898, J. B. Miller held the post of senior assistant at Town's Hospital, Glasgow, and then settled in general practice on the Lanarkshire border, in the valley of the Clyde. Bishopbriggs—its name coming down from pre-Reformation days—is only 15 minutes by bus from Glasgow Cross, but it is the centre of the mining and agricultural community among whom Miller found his lifework. In 1909 he proceeded to the M.D., again with commendation, and he also took the D.P.H. Besides being a general practitioner he was also a medical officer of health—for his native burgh of Kirkintilloch and for Kilsyth in Stirlingshire, both of them only a short distance from Bishopbriggs. He always took his public health duties seriously, and some years ago he wrote a useful article about the importance of the general practitioner as a health educator. A leading figure in the district in which he lived and worked, Dr. Miller was a justice of the peace for the County of Lanark, a past chairman of the Bishopbriggs District Ratepayers' Association, chairman of the local Horticultural Society, a trustee of the Cadder and District Miners' and Community Welfare, and one of the oldest members of the Cadder parish church, being father of the kirk session. He was a district medical officer for the county of Lanark, medical officer to the Post Office, Admiralty surgeon and agent, and medical referee to the Department of Health. During the first world war he was medical officer in charge of the auxiliary Red Cross hospital in his own parish of Cadder. In course of time he found wider fields for his energies as chairman of the Scottish Colliery Surgeons Committee, chairman of the Lanarkshire Local Medical and Panel Committee, and member of the Central Midwives Board for Scotland. In 1951 Dr. Miller completed fifty years of practice in and around Bishopbriggs, and his friends and patients marked the occasion by making a presentation to him at a public gathering in Cadder Parish Church Hall. Last year, at the Annual Meeting of the B.M.A. in Glasgow, Dr. Miller's own university conferred on him the honorary degree of doctor of laws. Professor Stanley Alstead, presenting him for the degree, described him as "a master of this difficult art of general practice," and as "a physician who personifies those virtues which have made the Scots doctor a revered figure throughout the world."



Dr. Miller first became a representative when the British Medical Association held its Annual Meeting at Glasgow in 1922, and in 1929 he was elected a member of the Council. Then began a round of central committee work of which he took his full share, although for him every meeting entailed two nights or two days in the train. He was chairman of the Health Services Committee which preceded the Medical Planning Com-

mission, and on that Commission itself he did excellent service as chairman of the Co-ordination Committee, a task which exactly suited his abilities. He was also, at various times, a member of the Public Health Committee (for a quarter of a century), the Parliamentary Elections Committee, and an earlier General Medical Services Committee which shaped the Association's proposals for a general medical service for the nation. Again, particularly on questions of industrial practice, workmen's compensation, and national health insurance, his experience and counsel were often of service. His knowledge of both the general practice and the public health fields made him a useful member of the liaison committee which ensures co-operation between the Association and the Society of Medical Officers of Health.

In 1945 he was elected by the Representative Meeting in London as its chairman for 1946. His election took place on the very day that Mr. Attlee's Government came into power, and the three years which followed were the most strenuous in the Association's history. They saw the introduction of the National Health Service Act, the mobilization of the profession against some of its provisions, the plebiscites, the resumed negotiations, and the conditional agreement to enter the Service subject to an amending Bill. His term of office ended within a week of the measure coming into operation. During those three years seven Representative Meetings were held, four of them devoted entirely, and the other largely, to the question of the National Health Service. In a similar crisis a generation earlier, when National Insurance was introduced, there were nine meetings of the Representative Body in the course of twenty months, and the two men who filled the chair during that period, Sir Ewen Maclean and Sir Jenner Verrall, had a stormy passage. But the conflict was perhaps sharper in 1946–8. The Association was by this time twice as large, its Divisions were better organized, it was politically more alive, and the demand for leadership was more acute. As chairman of the Representative Body Miller was faced with agenda containing hundreds of motions from Divisions, many of them similar in purpose but with differences of phrase which might be important, at all events in the eyes of the Division which had sent them forward. To assign priority and to make rulings as to how far one motion might be held to cover others was both an arduous and a delicate task, calling all the time for the utmost alertness and power of analysis, the blending of authority with tolerance, and the exercise of good humour to dispel any rankling sense of injustice.

Miller's Scottish humour, which was not artificial or forced but an idiom that was natural to him, never failed him. Not once in that long period was he outwardly perturbed. If he had occasion to utter a rebuke it was done in so whimsical a way that the lesson remained but not the sting. He was always scrupulously fair. In spite of his own obvious desire to get through the tide of words to the rock of decision, he resisted importunate calls that the question be now put or that the meeting proceed to the next business if he thought the matter had not been sufficiently debated. He never failed to give the proposer of a motion the right of reply, while hinting to him either that there was nothing to reply to in the arguments against him, or else that the arguments were so overwhelming that he could not possibly have any reply to them. He once remarked that the business of the Representative Meetings was got through thanks to a core of experienced representatives who never appeared on the platform and who had made up their minds uninfluenced by eloquence of any sort.

Dr. Miller underwent a serious operation in 1948, but in a surprisingly short time he was back again at Headquarters, looking rather more frail, but with mental energies unimpaired and a wit as sharp as ever. His recreations were golf and curling, gardening and field botany, and archaeology, for which last there is plentiful material in north-west Lanarkshire. Dr. Miller married Margaret Vaughan, daughter of the Rev. I. B. A. Watt, and he is survived by his widow, one son, and two daughters. Brownswood, Bishopbriggs, was a very happy home, and Dr. Andrew Blakely Miller and Dr. Marjory Buchan Miller, both of the Glasgow medical school, helped to carry on their father's practice there.

The CHAIRMAN OF COUNCIL, Dr. E. A. Gregg, writes: With the death of "J. B." a familiar and much-loved figure passed away—one of the old guard. He was a man of inflexible principle and great integrity and held in very high regard by all of us. His common sense and realistic approach to all problems was characteristic of all his contributions to debate, whether in Council or committee. His humorous asides and interjections during his chairmanship of the Representative Meetings were a delight and often a great help at a difficult moment.

Dr. J. B. Miller found the life of a family doctor a satisfying and good one, and he had no use for moaners and grumblers. There must be a great number who found in him a friend and helper in their troubles and illnesses, whose kindly ministrations will long be remembered. All his friends rejoiced with him when his old university conferred upon him the honorary degree of LL.D. during our meeting in Glasgow. He loved to recall his early days as a student, and his speech—a special one of his—when he described the old "bone" room and many of the incidents of those days was a sheer delight to us all.

We can ill afford to lose men such as "J. B." His memory and his influence on B.M.A. affairs will continue for a long time to come.

The CHAIRMAN OF THE REPRESENTATIVE BODY, Dr. I. D. Grant, writes: By the death of James Blakely Miller the West of Scotland has lost an outstanding personality. "J. B.," as he was known affectionately to his innumerable friends, was essentially a B.M.A. man. During a long and happy life he had cultivated many interests and hobbies, and the demands of a busy practice were not easily satisfied. But, despite all these activities, the welfare of the B.M.A. was always his first consideration. He occupied almost every high office of the Association in Scotland, and when in 1954 his Alma Mater conferred upon him the degree of LL.D. his colleagues, even more, I think, than himself, were gratified at the honour which was given to a most erudite and greatly loved general practitioner.

As chairman of the Representative Body, even though his health was failing a little, he made the long journey to London gladly and unsparingly. He played his full part in all the committees of the Association, and his charm of manner and pawky humour quickly won him the affection as well as the regard of his colleagues in the south. I well remember the first occasion on which he took the chair. Some representatives at an early stage of a bleak and foggy morning were just a little intolerant of the rather boring speaker. "J. B." appealed to the meeting: "You might perhaps allow him to go on. We are rather anxious to fill in the time anyhow, as the Birmingham train is an hour late."

He served on the Medical Planning Commission in 1940 and was largely responsible for many of the constructive suggestions made by that body for an improved medical service, but which, unfortunately, were not implemented by the politicians who eventually introduced the National Health Service. Like so many of his generation, he did

not take kindly to nationalized medicine, and was happy to live in semi-retirement after the inception of the National Health Service.

As an after-dinner speaker he was unsurpassed, and the flights of fancy on which he embarked on these occasions will long remain a pleasing memory to those of us who were privileged to hear him speak. However, the most outstanding service he rendered to the Association was one of which he himself was quite unconscious—that was his influence over his younger colleagues and his ability to arouse in them a desire to take part in B.M.A. work. By precept and example he showed us how much one man could do in the service of his fellows. He had a genius for friendship, and I do not think he had a single enemy. We know that the salutation which awaits him is, "Well done, thou good and faithful servant."

Dr. GUY DAIN writes: A Scot with so many of the good qualities of his race, J. B. Miller was not easily provoked to speech, but when he spoke it was with both wisdom and wit. He could, and frequently did, provide the short, snappy, and completely appropriate comment in the course of a discussion, and not infrequently when in the chair of the Representative Body. His speech proposing the health of the chairman of the R.B., then Sir Henry Brackenbury, was a masterpiece of humour and sly fun. But then he was to the B.M.A. over a long spell of years a wise counsellor and leader whose advice was always the result of careful thought and balanced judgment. For those of us who for so long have been associated with him in the work at Headquarters, his cheerful friendship and always helpful advice will be a great loss.

H. W. BARBER, M.B., F.R.C.P.

British dermatology was bereft of two eminent figures on the same day, January 13—Dr. H. W. Barber, of Guy's, and Dr. W. J. O'Donovan, of the London Hospital, to whom an obituary tribute appears on the next page. Both men were born in the same year. The careers of both in their first hospital appointments were interrupted by service in the first world war. Both gained a high reputation in dermatology and made contributions to its literature. Both were in consulting practice in the Harley Street area, within a couple of hundred yards of each other. Both became presidents of the Section of Dermatology of the Royal Society of Medicine. Dr. Barber, unlike Dr. O'Donovan, confined his activities to his profession and did not enter public life, but among his dermatological colleagues he was recognized as one who spoke with authority and out of wide experience. In the Dermatological Section, which every month holds a clinical discussion on a series of cases, Dr. Barber was a constant contributor, bringing forward unusual cases of his own and commenting in his thoughtful and often provocative way on the cases of others.

Harold Wordsworth Barber, the son of a Nottingham solicitor, was born on May 13, 1886. He was educated at Repton, and from there went on with a scholarship to Clare College, Cambridge, obtaining first-class honours in the Natural Sciences Tripos in 1908. His medical training was taken at Guy's, with which hospital he was associated until the end of his life. He graduated M.B., B.Ch. Cambridge, in 1911. In the following year he obtained the Arthur Durham Travelling Scholarship of Guy's, which enabled him to study dermatology in Paris and also at Hamburg, where he learned from the celebrated dermatologist, Professor Unna. He returned to be medical registrar at Guy's from 1913 to 1915, and took the M.R.C.P. at this time. In the first world war he joined the R.A.M.C. for service in India, Mesopotamia, German East Africa, and France. After the war he returned to his registrarship at Guy's and in 1919 was appointed physician to the skin department. From this time onwards he quickly made his reputation in the specialty he had chosen. He remained on the active staff of his hospital until 1951, when he became consultant to the department. He was also consulting dermatologist to the Royal Navy, and served at various times on the honorary staffs of the Prince of Wales and the Evelina Hospitals. A past-president of the British Association of Dermatology, he was a corresponding member of the French, German, and Vienna Dermatological Societies. He became Fellow of the Royal College of Physicians in 1922. His Lettsomian lectures to the Medical Society of London in 1929 were on the subject of "Dermatology in Relation to other Branches of Medicine" and were published in a shortened version in this *Journal*. At the Annual Meeting of the B.M.A. in 1932 Barber was president of the Section of Dermatology and Venereal Diseases. He contributed to the journal's numerous papers on dermatological and more general medical subjects, and was responsible for the section on diseases of the skin in Taylor and Poulton's *Medicine*. In 1952 he gave the Prosser White Oration.

He married Juliette Louise, daughter of Madame Veuve Champrenand, of Paris; they had no family.

We are indebted to Dr. L. FORMAN for the following appreciation: The passing of Dr. H. W. Barber will give deep sorrow to his friends, his colleagues, and to the large number of patients who were grateful for his skill and sympathetic understanding. He was one of the best known of British dermatologists at home and abroad. Visiting dermatologists to this country would always be found at some time or another in Dr. Barber's clinic at Guy's, and they had great respect and affection for him. Indeed, he was a worthy representative of the medical profession. Impressive and handsome of appearance, he kept his youthful figure and carriage to the last. He was fluent in conversation, and his intellectual quality and capacity were soon apparent.

His interests were wide, and in all of them a tenacious memory and an active interest enabled him to discourse on literature, the theatre, racing, cricket, and other sports. On all these subjects his views were original, occasionally iconoclastic, and revealed the consideration of a contemplative man on the trends and achievements of this century.

Dr. Barber began his postgraduate career as a general physician, and was a most successful medical registrar at Guy's at a time when there were only two registrars in the medical wards; all those who were in the wards at that time testify to his ability and the facility with which he could impart his knowledge. It was with this background of general medical knowledge and training that he approached dermatology, and it gave him the ability to excite the interest of students and postgraduates in the specialty. His careful and minute study of the skin lesion was integrated with his assessment of the patients' personality and medical status in a way that can rarely have been equalled. His

opinion was an excellent one, based on a wide reading in medicine, and his management of the case was a model in the art of therapy.

Dr. Barber wrote fluently and well. He anticipated and stimulated much of the work indicating the importance of disorders of metabolism, endocrine changes, psychological disorders, and chronic infection in the genesis of skin reactions. Of his numerous writings two give the measure of his comprehensive approach and grasp of the problems of medicine and well repay frequent reading. The first is the Lettsomian Lectures, already referred to, and the second, his Prosser White Oration, "What is Truth?" published in the *Transactions of the St. John's Hospital Dermatological Society* in 1953.

Those of us who were trained by Dr. Barber will be ever grateful for the experience. He could make one see and understand. His knowledge of the fundamentals of medicine and of dermatology enabled him to present every case in a manner that provoked interest and thought and a determination to enlarge one's knowledge and experience. To his juniors he was kindness itself, and took the greatest pleasure in their progress and success. He never condescended, and was eager to refer to the observations and publications for which they were responsible. Dr. Barber's contributions to medicine will not be ignored, and in our hearts he will live. To his widow we extend our deepest sympathy.

A. E. S. writes: When I first went into the wards at Guy's H. W. Barber was a medical registrar. He was a quiet, charming personality. In many rounds with him, one in particular is remembered. He talked about agnosia, alexia, etc. He said that in reading up any subject it was well to read it in as many books as possible. I have seen him on many occasions since and have been his patient. He was admired and respected by all.

W. J. O'DONOVAN, O.B.E., M.D., M.R.C.P.

The death was announced on January 13 of Dr. W. J. O'Donovan, who was for a quarter of a century physician in charge of the skin and phototherapy departments of the London Hospital and lecturer on diseases of the skin and on syphilis at the Medical College. Dr. O'Donovan was well known in many spheres—medical, political, and religious—and in all of them his ebullient personality, his wit and repartee, and his good-humoured zeal in controversy made a marked impression.

William James O'Donovan was born in Kent in 1886, but his family was from County Cork. He was a student at London University, entering the London Hospital Medical College in 1905 and qualifying in 1909. He graduated M.B., B.S. in 1911, proceeded M.D. in 1913, and took the M.R.C.P. in 1914. After qualification he held for over a year the post of pathological assistant at his hospital and at a later period he was for some time junior assistant director at the pathological institute there. During the first world war he was chief medical officer to the Ministry of Munitions, and for his services was made O.B.E. in 1920. He went on to widen his experience in general medicine and surgery and then returned to the London as first assistant in the skin and light department. In his early days as physician he had charge of the syphilis block and later of the syphilis out-patient clinic until a separate venereal diseases clinic was established under the authority of the London County Council in 1930. After a quarter of a century at first as assistant physician and then as physician he retired in 1952.

A well-known dermatologist, O'Donovan combined with his dermatology an interest in pathology, in order, as he said, to prevent himself from becoming what his chief, J. H. Sequeira, once described as a "pimple doctor." At one time he was coroner's pathologist for London. Perhaps his most outstanding contribution to dermatology was his exposition of emotional factors in skin disease. This aspect was much neglected by physicians thirty years ago when he wrote his *Dermatological Neuroses*. A considerable textbook of his on *Diseases of the Hair* was written in a fortnight. He made contributions on a wide range of subjects, including industrial dermatitis and cancer and T.N.T. poisoning (he was a member of the Government T.N.T. Committee). For a time he assisted in the editorship of the *British Journal of Dermatology*. He was consulting physician to the skin department of Queen Mary's Hospital, Stratford, and to a number of other hospitals; consulting dermatologist to Dr. Barnardo's Homes; and lecturer at the London Institute of Dermatology, St. John's Hospital. In the second world war he served in the R.A.M.C. from 1939 to 1945, when he was released with the rank of lieutenant-colonel. He held the appointment of adviser in dermatology to the Middle East Forces in Egypt and Palestine. He was an assistant examiner in medicine in the University of London, and in 1952 he was elected a representative of the Faculty of Medicine on the standing committee of convocation of the University.

[*Elliott and Fry*

For seven years Dr. O'Donovan was honorary secretary of the Marylebone Division of the British Medical Association, for two further years its chairman, and for four years he represented it in the Representative Body. In 1933 at the Annual Meeting at Dublin he was president of the Section of Dermatology, and in 1939–41 president of that section of the Royal Society of Medicine.

During the general strike of 1926, when the electricity supply to the London Hospital was cut off, his energetic and public protest brought him with a bound into national politics, and in 1931 he was returned to Parliament as Conservative member for the Mile End division of Stepney, in which the London Hospital stands. His reversal of a 6,000 Labour majority was a tribute to his personality rather than an endorsement of his politics; he failed to hold the seat at the General Election in 1935, and was similarly unsuccessful in 1950 in opposing Dr. Edith Summerskill in West Fulham. He did not fit very well into Parliament. He was not able, as the members of the old Nationalist party were, to adapt his Irish exuberance to the constraints of Parliamentary procedure, but on the political platform, especially with an antagonistic audience, he was in his element. He occupied various positions of prominence in the Conservative Party, and was president of the University of London Conservative Association.

Dr. O'Donovan was a devout Catholic, and never hesitated to introduce Catholic doctrine into medical or political discussions. For more than 30 years he was honorary secretary of the Guild of St. Luke, SS. Cosmas and Damian. In 1951 he received from the Pope the

honour of the Knighthood of St. Gregory the Great. Just before the second world war he was appointed by the Cardinal Archbishop of Westminster the leader of Catholic Action in England.

He married Ethel K. Smith, who was a great help to him in his professional and public life, and they had one son and two daughters.

We are indebted to Dr. BRIAN RUSSELL for the following appreciation: Dr. O'Donovan succeeded Dr. Sequeira as physician to the skin department at the London Hospital in 1926 and held the post for 26 years. The esteem in which he was held was indicated by a following of 70 students and doctors on his last teaching round. He had an extensive training in general medicine and pathology before taking up dermatology, and he always maintained a practical interest in morbid anatomy, holding that the post-mortem table was as conducive to right thinking and the pursuit of truth as laboratory work at a teak bench. During the second world war he served in the Middle East, and those who trained with him at Tidworth will never forget the zest with which he applied himself to adjustment from civilian to military habits.

Dr. O'Donovan will be remembered as one of the great personalities of the medical profession during the first half of the twentieth century. He had an ebullient mind with ready wit and unfailing repartee suitable for every occasion. He was more interested in sick people with their skin affections than in hair-splitting arguments over individual spots and pimples: he believed in the importance of emotional factors in the genesis of many common dermatoses, and worte a short monograph, *Dermatological Neuroses*, in 1927 which was the prototype of much writing on dermatology from its psychiatric aspects.

Those who were fortunate enough to attend his political meetings will never forget his oratory and ability to cope with hecklers, which soon earned him the right to sit in Westminster. Hearing him giving evidence in court made one think that he might have made just as successful a career in the legal profession as in medicine. Always cheerful in adversity, he could joke about his own illness even after the first of the three episodes which progressively struck him down. All those who have enjoyed his quips and sallies, and who have thus found the acquisition of knowledge less tedious, owe a debt of gratitude to this irrepressible and irreplaceable personality for having observed when he first came to the London Hospital the inscription over the Medical College doorway, *Amara lento tempera risu*, which may be very freely translated, "Temper the bitter things of life with a smile."

Dr. PATRICK HALL-SMITH writes: I should like to pay tribute to the late Dr. W. J. O'Donovan, with whom I was closely associated, first in the Army, and then as his senior registrar at the London Hospital. In the difficult years just after the war no young dermatologist could have served a more stimulating or considerate chief, and many besides myself owe their careers to his championship and guidance. "O'D," as he was popularly known, had a great presence and a truly sparkling personality; he was a gifted and original speaker, possessing a lively forensic skill in argument. Always an individualist, he wore a scarlet-lined cloak during his Army service, and discomfited a series of inspecting generals who imagined they were conversant with military law. Hecklers at West Fulham in the 1950 election also found the contest unequal. His learning and intellect were apparent, but those who knew him well recognized too a man of strong faith and courage. Generations of old-Londoners will recall him as an exceptional clinician and teacher, and as one who was never dull; his colleagues in dermatology mourn a unique and lovable personality whose provocative statements enlivened many a dreary meeting. He will not be forgotten, and his writings will live on as an important contribution to British dermatology.

G. V. ANREP, M.D., D.Sc., M.Sc., F.R.S.

Dr. G. V. Anrep, professor of physiology in Fouad I University, Cairo, died in Cairo on January 9, aged 63.

Gleb V. Anrep was born in St. Petersburg, the son of Basil von Anrep, who studied the action of cocaine and in 1880 suggested its use as a local anaesthetic. From the University of Dorpat he went on to study medicine in St. Petersburg. Before qualifying in medicine in 1914 he worked for a time as demonstrator of physiology in the Military Medical Academy at St. Petersburg, and he had also visited London and worked in the physiology department of University College. During the war he served as a medical officer in the Russian Army until 1917 and then returned to St. Petersburg as senior assistant in physiology at the Institute of Experimental Medicine in that city. He joined the forces of General Denikine, who fought against the Bolsheviks, and not long afterwards he had to leave Russia. Settling in London, he was first appointed assistant, then in 1923 senior assistant, and finally in 1926 reader in physiology at University College. He obtained the D.Sc. degree in physiology in 1923 and was awarded the Schäfer Prize and William Julius Mickle Fellowship two years later. He became a naturalized British citizen in 1925. Before going to Cairo as professor of physiology in 1931 he was for a time a lecturer in physiology at Cambridge, and also Cooper-Lane lecturer at Stanford University, San Francisco. He was elected F.R.S. in 1928.

Most of Anrep's studies were on the circulation, and he published numerous articles in the *Journal of Physiology*, the *Proceedings of the Royal Society*, and other journals. His Lane Medical Lectures were published in book form in 1936 under the title *Studies in Cardiovascular Regulation*. Anrep was a former pupil and collaborator of Professor Pavlov, and in 1927 he translated and edited Pavlov's book, *Conditioned Reflexes*, which had been published in Russian in the previous year. This was a most important piece of work, for it was the first time that a full account of Pavlov's researches had appeared in the English language. Apart from the ordinary difficulties of translation, Anrep had to cope with an entire new terminology. The result was remarkably successful.

G. H. G. writes: G. V. Anrep was a pupil of Pavlov and played an important part in making conditioned reflexes known outside Russia. He had paid a short visit to University College, London, before the first world war, and came back there in 1918 owing to political events in Russia. He thus came under the influence of Starling, and soon showed that he was a skilful experimenter who could make heart–lung preparations more rapidly than other people. He published a series of papers on the metabolism of the salivary glands and on the regulation of the circulation. With Starling, and with other people, he carried out elaborate experiments such as the perfusion of the head and neck by means of a heart–lung preparation, and worked out details of the reflexes controlling the circulation. He was elected F.R.S. in 1928 at the early age of 37. At about this time he added much to our knowledge of the coronary circulation and the circulation in voluntary muscles, proving that the actual contraction of the muscles caused a stoppage of the flow, and recording the reactive hyperaemia which followed even when the flow was stopped for a fraction of a second. This work is summarized in the Lane Medical Lectures which he gave at Stanford University in 1936.

In Egypt Anrep became interested in histamine, and published a series of papers with G. S. Barsoum and others

on the physiology of this substance. He was the first to show that normal urine contains not only free histamine but also inactive conjugated histamine, and that this comes from the intestine. He discovered the first histamine-releaser, tubocurarine.

He was proud of his British nationality, but this cannot have helped him when, a few years ago, his career was again interrupted by political events and he had to give up work in the laboratory. He was an energetic and enterprising person with many interests. He learned Arabic well enough for intelligent discussion of the world's affairs. He drove an old Ford car on expeditions across the desert which more cautious people regarded as foolhardy. He was an enthusiastic philatelist who had an arrangement with postmasters in Cairo which led to the discovery of what he called "the Anrep variations." He was very good company and fond of telling dramatic tales about himself; it is sad that we shall hear him no more.

Sir ARTHUR KEITH, M.D., LL.D., D.Sc. F.R.C.S., F.R.S.

Dr. F. PARKES WEBER writes: Everyone knows of Sir Arthur Keith's enthusiasm in regard to the collection of skulls when he was conservator of the Museum of the Royal College of Surgeons, London. He was not contented with one specimen of the skulls of any particular class of natives, but preferred to have a considerable number for purposes of comparison. Shortly before the first world war a cousin of mine, who was somewhat of an amateur anthropologist, lived in a flat close to the British Museum. He possessed a small collection of skulls of the aborigines of a small island in Oceania. As he was going to be married he wished to get rid of these skulls in deference to the wish of his fiancée. He thought of presenting them to the collection of Sir Arthur Keith. The latter invited my cousin to dinner with him at a Holborn restaurant, in order to discuss the matter. After the meal Sir Arthur said to my cousin: "If you don't give me those skulls I'll have yours." This so tickled the fancy of my cousin that, if he had not already made up his mind, he decided to present the collection to the Royal College of Surgeons. Subsequently, after my cousin had returned from Salonika, where he had served during the war, I saw a good deal of him and he told me the above story.

A memorial service for the late Sir ALFRED B. HOWITT, C.V.O., M.D., will be held in the chapel of St. Thomas's Hospital, London, S.E.1, at 12.15 p.m. on Thursday, January 27.

Medico-Legal

BABY'S DEATH FROM BORON POISONING

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

On November 23, 1954, the inquest was concluded at Ealing before Mr. H. G. Broadbridge, coroner for West Middlesex, on a 3-months-old baby boy called Tony Smith, who died on September 28, 1954, from boron poisoning.

The baby had been a little sore about the buttocks and between the legs. His mother asked in a chemist's shop for a boracic powder and told the chemist what she wanted to use it for. She was sold some powder in a little cardboard drum. The powder had no smell and the child's grandmother thought that the drum was labelled "boracic acid powder."

After the powder had been used for about a week the baby seemed ill, and on September 19 he was admitted to Hillingdon Hospital suffering with severe vomiting and diarrhoea. He also had a ruptured navel. Three days later Dr. H. V. L. Finlay, the paediatrician at Hillingdon Hospital, diagnosed poisoning by boracic acid, and the whole skin, including that inside the nose and mouth, began to peel. The boron content of the urine was found to be 28.7 mg. per 100 ml. Six days later the baby died.

In evidence Dr. Finlay said that the raw condition of the baby's napkin area on admission to hospital was ideal for the absorption of boric acid. He had never seen any harmful effects from the use of boric acid preparations, but emphasized the danger of using pure boracic acid in powder form, and thought it should not be sold indiscriminately over the counter.

Dr. Donald Teare, who made the post-mortem examination, found the boric acid content of the brain to be 13 mg. per 100 g., of the lung to be 28 mg. per 100 g., and of the kidney to be 33 mg. per 100 g., which together with the amount in the urine previously estimated was within the range in which boron poisoning occurs. Dr. Teare said that ordinary powders sold for babies usually contained 5 to 10% of boric acid, and that of the 37,000 necropsies he had made this was the first occasion on which he had found boric acid poisoning. He thought that what had happened was that the baby's mother had been sold neat boric acid as a powder.

A verdict of death by misadventure was recorded.

Vital Statistics

Influenza

A few more outbreaks of virus-B influenza had been reported up to January 17, and the increases in the weekly claims on the Ministry of Pensions and National Insurance suggest a greater prevalence among adults. In London reports of sickness indicate the probable presence of influenza, and in the environs the situation is much the same. In the northern half of the country and in Wales the disease is waning; in the southern half it is still advancing here and there, particularly in the eastern region, but progress is slow. Clinically the infection is usually mild. Laboratory reports continue to confirm most of the outbreaks as being due to virus B, but two patients in the midlands have been proved to be suffering from a virus-A infection. No spread from either has been traced.

Smallpox in France

A message from the French Ministry of Public Health and Population, dated January 8, reports the number of cases of smallpox in the Vannes area as 25, including two deaths, though a press report from Paris dated January 12 gives the number of cases as 40, including 4 deaths. The first case occurred at the beginning of December, 1954, in an unvaccinated child aged 1 year. The child's father had returned 10 days previously from military duties in Indo-China, where he had been in a hospital in which cases of smallpox were being treated.

Causes of Death in June Quarter

In England and Wales in the June quarter deaths from respiratory tuberculosis (1,657) were 9% fewer than in the corresponding period of 1953. Cancer deaths were slightly more—21,826 as compared with 21,451; but deaths from cancer of the uterus (888) were 12% below those in the second quarter of 1953. Accidental deaths rose to 3,633 (3,272 in June quarter, 1953). This was mainly accounted for by increases in accidental poisoning (243 deaths compared with 177 a year earlier), falls (1,249 compared with 969), and burns (166 compared with 146). The number of suicides (1,415) was the highest since the June quarter, 1939.

England and Wales Population

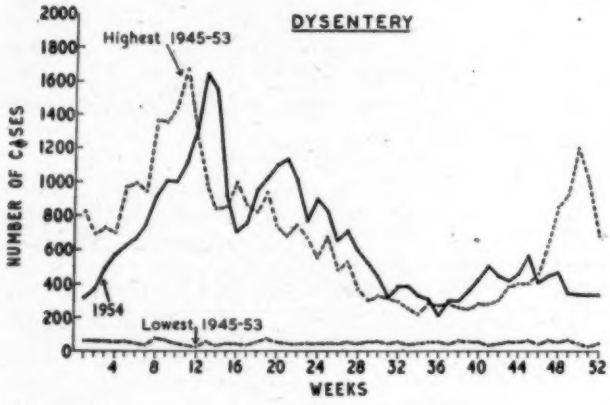
The home population of England and Wales has increased by over 500,000 since census day (April 8, 1951), according to the Registrar-General's estimates published in the Return for the September Quarter, 1954. It is given as 44,480,000 (21,492,000 males and 22,988,000 females).

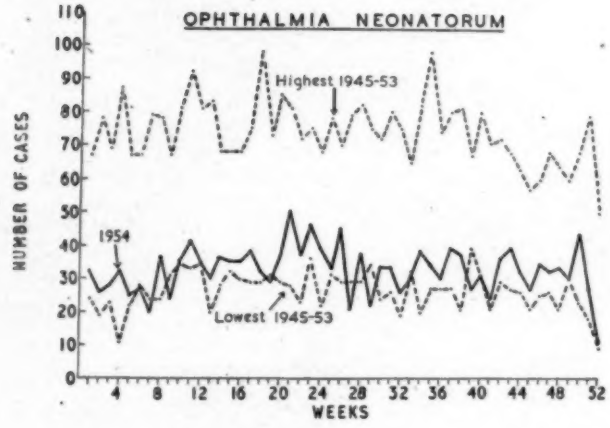
Week Ending January 8

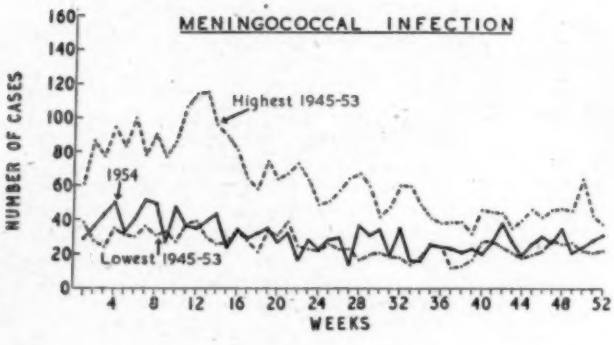
The notifications of infectious diseases in England and Wales during the week included : scarlet fever 463, whooping-cough 1,791, diphtheria 13, measles 9,385, acute pneumonia 1,135, meningococcal infection 42, acute poliomyelitis 25, dysentery 346, paratyphoid fever 4, and typhoid fever 4.

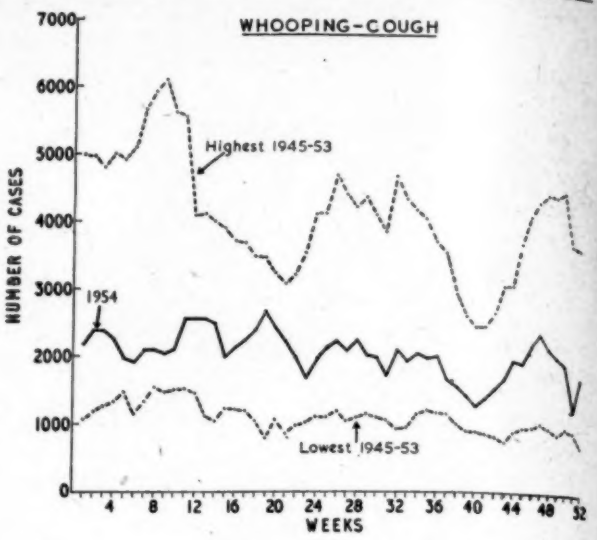
Graphs of Infectious Diseases

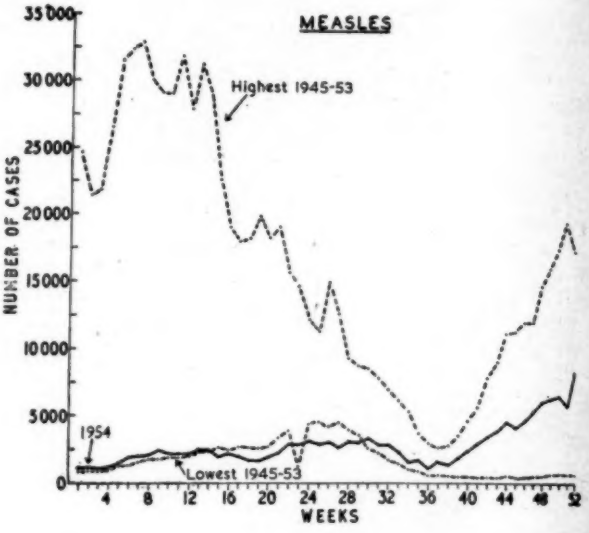
The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1945–53 are shown thus - - - - - -, the figures for 1954 thus ————. Except for the curves showing notifications in 1954, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.

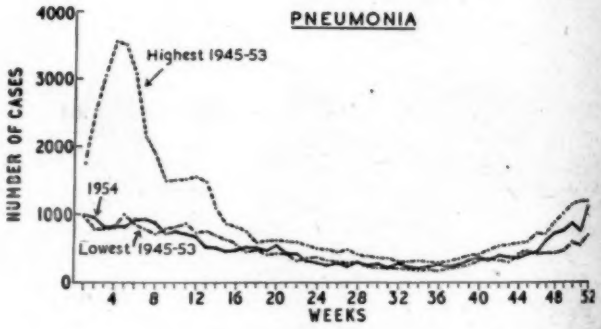


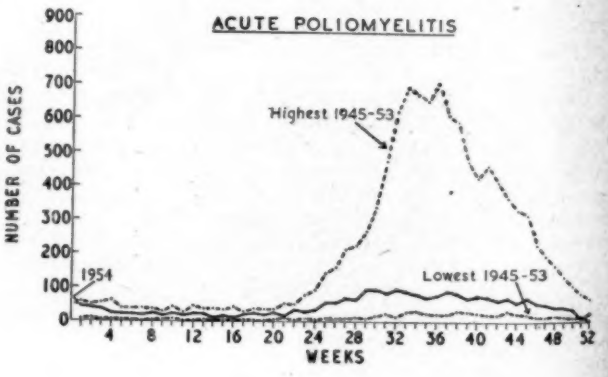


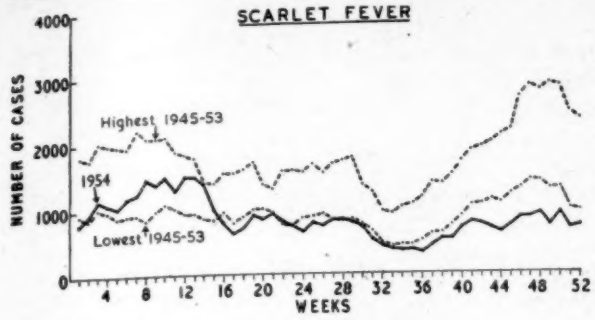


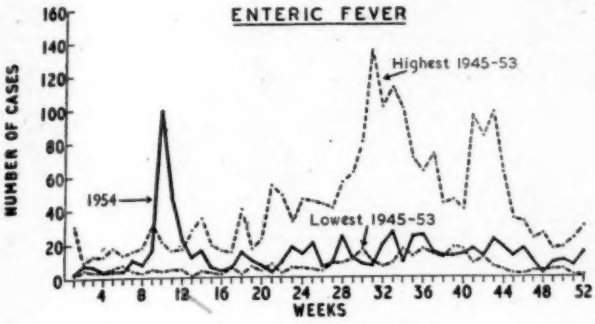


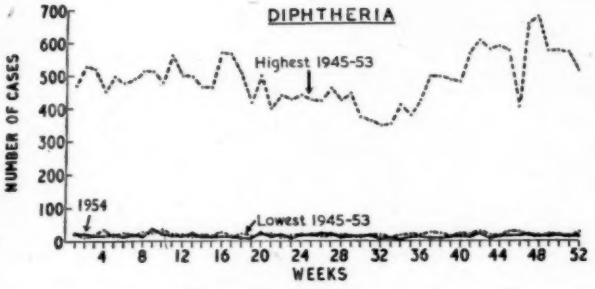












Infectious Diseases

A rise occurred in the incidence of infectious diseases in England and Wales during the week ending January 1. The increases in the number of notifications included 2,480 for measles, from 5,840 to 8,320, 466 for whooping-cough, from 1,256 to 1,722, 352 for acute pneumonia, from 756 to 1,108, and 34 for scarlet fever, from 673 to 707.

The largest increases in the incidence of measles were 598 in Lancashire, from 1,912 to 2,510, 438 in London, from 550 to 988, 228 in Essex, from 341 to 569, 159 in Derbyshire, from 69 to 228, 155 in Warwickshire, from 172 to 327, 145 in Yorkshire West Riding, from 558 to 703, and 122 in Durham, from 306 to 428. The largest rises in the number of notifications of whooping-cough were 56 in Lancashire, from 127 to 183, and 50 in Durham, from 85 to 135. Only small variations were reported in the local trends of scarlet fever. 13 cases of diphtheria were notified, being 2 fewer than in the preceding week. The areas with multiple cases of diphtheria were Lancashire, Liverpool C.B. 4, Warwickshire, Birmingham C.B. 3, Surrey, Epsom and Ewell M.B. 2.

23 cases of acute poliomyelitis were notified; these were 13 more for paralytic and 1 more for non-paralytic cases than in the preceding week. The largest returns were London 5 and Middlesex 3.

340 cases of dysentery were notified—the same total as in the two preceding weeks. The chief centres of infection were London 57 (Hackney 17, St. Marylebone 11), Norfolk 57 (Norwich C.B. 41), Lancashire 56 (Oldham C.B. 14, Liverpool C.B. 13), Yorkshire West Riding 24, Warwickshire 18 (Birmingham C.B. 17), Lincolnshire 18 (Scunthorpe M.B. 18).

82 deaths were attributed to influenza in the great towns, a rise of 26. The largest totals were Manchester C.B. 8, Birmingham C.B. 7, Nottingham C.B. 6, Wolverhampton C.B. 5.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **January 1, 1955** (No. 52), and corresponding week 1953–4.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1954–5					1953–4				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	13	1	3	0	2	29	3	3	0	
Dysentery	340	57	175	10	5	340	52	105	3	13
Encephalitis, acute	4	0				4	1	0	0	
Enteric fever:										
Typhoid	4	1	1	0	0	1	0	0	0	
Paratyphoid	11	1	2	0	0	0	0	0	0	
Food-poisoning	131	18				127	18		0	
Infective enteritis or diarrhoea under 2 years				11	8				16	22
Measles*	8,320	988	241	496	59	1,327	9	13	8	101
Meningococcal infection	31	1	13	0	1	27	2	8	3	1
Ophthalmia neonatorum	11	0	5	0		18	2	4	0	
Pneumonia†	1,108	71	200	5	2	907	58	297	13	2
Poliomyelitis, acute:										
Paralytic	21	5	3	0	2	40	2	6	1	8
Non-paralytic	2	0				13	0			
Puerperal fever§	196	25	4	0		228	34	9	0	
Scarlet fever	707	51	134	40	16	1,111	70	166	42	32
Tuberculosis:										
Respiratory	526	59	131	26				120	30	
Non-respiratory	84	10	23	4				23	7	
Whooping-cough	1,722	108	103	33	7	2,284	84	261	66	99

DEATHS in Great Towns	1954–5					1953–4				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	1	0	0	0	0	0
Dysentery	0	0	1	0		0	0		0	
Encephalitis, acute	0	0			0		0			0
Enteric fever	1	1	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	6	0	0	0	1	16	0	0	0	0
Influenza	82	2	2	0	2	22	6	1	0	0
Measles	0	0	1	1	0		0	0	0	0
Meningococcal infection	0	0	1				1	1		
Pneumonia	380	40	24	16	13	332	48	27	12	6
Poliomyelitis, acute	0	0			1	3	0			0
Scarlet fever	0	0	0	0	0		0	0	0	0
Tuberculosis:										
Respiratory	89	16	9	0	2	124	15	14	3	9
Non-respiratory			0	0	1		4	1	1	1
Whooping-cough	4	1	0	0	0	4	0	1	0	2
Deaths 0–1 year	246	12	37	8	17	290	42	36	13	18
Deaths (excluding stillbirths)	6,745	894	681	118	168	6,767	1022	647	158	183
LIVE BIRTHS	7,337	2158	844	232	300	8,227	1222	823	229	365
STILLBIRTHS	201	42	23			201	27	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Association of British Pharmaceutical Industry.—The Association of the British Pharmaceutical Industry celebrated its 25th anniversary last week by publishing a booklet describing the history and work of the association and by holding a reception which was attended by the Minister of Health, Mr. IAIN MACLEOD, and his Parliamentary Secretary, Miss PAT HORNSBY-SMITH. Mr. J. F. BOUCHER, the president of the A.B.P.I., made a short speech at the reception, introducing the Minister. Mr. MACLEOD said that when he heard that the A.B.P.I. was holding its reception in the Great Hall of B.M.A. House he thought of his own position as being rather like Daniel accepting an invitation to be chief guest in the lions' den. Referring to the resentment which some people felt about Treasury control and investigations, Mr. Macleod said that such investigations were inseparable from a national health service. An industry of the importance and with the achievements of the British pharmaceutical industry had no need to fear these investigations. He himself was very conscious of the contribution the industry made to the life and health of the nation.

Ceremony at Nuffield Orthopaedic Centre.—On January 4 portraits of Lord Nuffield and the late Mr. G. R. Girdlestone, F.R.C.S., were unveiled at the Nuffield Orthopaedic Centre, Oxford, by the Vice-Chancellor of the University, Mr. A. H. SMITH, and Professor J. TRUETA (in the absence of Lord Nuffield). Speaking at the ceremony, Sir ROBERT MCCARRISON said that, not long after qualifying, Mr. Girdlestone had injured himself in a motor-cycle accident, and after this he decided to devote his life to the care of cripples. His work extended steadily, but by 1930 the huts of the orthopaedic centre were beginning to deteriorate. Lord Nuffield had then provided money to rebuild the hospital, and it was reopened in 1933 as the Wingfield-Morris Orthopaedic Hospital. Mr. Girdlestone always had a feeling of mission in life; he had not only got the hospital going but had imprinted on it his own spirit of service, friendliness, and happiness. Professor TRUETA said that Lord Nuffield and Mr. Girdlestone had met early in their lives. Although different in temperament and ideals, between them they had been able to make the hospital what it was to-day. The portrait of Lord Nuffield, by John Whalley, was presented by Lady Nuffield. Mr. Girdlestone's portrait, painted from a photograph by Frank Eastman, was subscribed for by patients and friends.

E.B.S. at Work.—The Emergency Bed Service invites all hospital admission officers in the Greater London area to visit the service's operations room at Fielden House, 28, London Bridge Street, London, S.E.1, to study its work. An appointment should be made by telephone (HOP 7181).

Sir Allen Daley has been elected chairman of the National Association for Maternal and Child Welfare.

COMING EVENTS

Liverpool Medical Dinner.—The annual dinner for past and present medical students of Liverpool University will be held on February 3 at the Bluecoat Hall, Bluecoat Chambers, at 7.30 for 8 p.m. Mr. A. A. GEMMELL, P.R.C.O.G., will be the guest of honour. Tickets (21s.) from H. DINNICK, Medical School, Liverpool.

Hunterian Oration.—Sir CECIL WAKELEY, Bt., will deliver the Hunterian Oration at 4 p.m. on February 14 at the Royal College of Surgeons, Lincoln's Inn Fields. He will speak on "Hunter and Surgical Research."

Fourteenth International Congress of Pure and Applied Chemistry.—The congress, which covers organic chemistry, will be held in Zurich from July 21 to 27. All those wishing to participate are asked to notify the secretary-general, XIVth International Congress of Pure and Applied Chemistry, Zurich, 1, Switzerland, not later than February 15.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Saturday, January 22

INSTITUTE OF ORTHOPAEDICS.—10 a.m., clinical demonstration by Mr. D. Trevor.

Monday, January 24

INSTITUTE OF PSYCHIATRY.—5.30 p.m., Dr. E. Stengel: lecture-demonstration.

MEDICAL SOCIETY OF LONDON.—8.30 p.m., discussion to be introduced by Mr. D. MacG. Jackson and Dr. W. M. Levitt: Burns and their Treatment.

Tuesday, January 25

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. Janet Vaughan: Radiation Effects on Bone.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: Lupus Erythematosus.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Wright-Fleming Theatre, 5 p.m., Dr. J. D. S. Flew: Induction of Labour.

Wednesday, January 26

BIRMINGHAM MEDICAL INSTITUTE: SECTION OF PSYCHIATRY.—8 p.m., Dr. M. S. Jones: Concept of a Therapeutic Community.

HARVEIAN SOCIETY OF LONDON.—8.15 p.m., annual general meeting. Presidential Address by Dr. R. Cove-Smith: Fitness, Facts and Fallacies.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Pathology of Lupus Erythematosus.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—5.30 p.m., Professor F. C. Ormerod: Types of Deafness.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Dr. C. E. Dukes: Pathology of Calculous Disease.

NOTTINGHAM MEDICO-CHIRURGICAL SOCIETY.—8.30 p.m., Mr. J. H. Kellgren: Rheumatism.

SOCIETY OF CHEMICAL INDUSTRY: FOOD GROUP.—At Chemical Society, Burlington House, W., 6.30 p.m., meeting of Nutrition Panel. Mr. E. M. Learmonth, M.Sc., F.R.I.C.: Soya in the Field of Nutrition.

Thursday, January 27

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Professor C. H. Gray: Chemistry of the Porphyrias.

GLASGOW UNIVERSITY MEDICO-CHIRURGICAL SOCIETY.—At Glasgow University Union, 7 p.m., Debate with Royal Medical Society.

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., Dr. A. S. Woodcock: Diagnosis of Gynaecological Conditions by the Examination of Smears; Dr. D. G. Miller: Diagnosis of Carcinoma of the Lung by Examination of the Sputum; Dr. J. H. Pettit: Histological Study of "Leucoplakia Vulvae."

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.30 p.m., Dr. Macdonald Critchley: The Body Image.

RENAL ASSOCIATION.—At the Ciba Foundation, 4.30 p.m., Mr. D. Innes Williams and Dr. R. Pugh: Renal Hypoplasias; Dr. S. W. Stanbury and Dr M. D. Milne: Base Losing Nephritis.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Mr. H. B. Stallard: Retinoblastoma Treated by Radon Seeds and Radium Disks.

ROYAL MEDICAL SOCIETY, Edinburgh.—At Glasgow, 8 p.m., debate with Glasgow University Medico-Chirurgical Society. Motion: That the Resident is the Cinderella of the National Health Service.

ST. ANDREWS UNIVERSITY.—At Physiology Department, Medical School, Small's Wynd, Dundee, 5 p.m., Dr. J. W. Smith: Postural Mechanism of Joints.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Dr. J. H. Paterson: neurology demonstration.

SOCIETY FOR ANALYTICAL CHEMISTRY: WESTERN SECTION.—At Bristol University, 7 p.m., Dr. E. Windle Taylor: Recent Advances in the Bacteriological Examination of Water.

Friday, January 28

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. S. C. Gold: Lupus Erythematosus.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., clinical demonstration by Mr. V. C. Thompson: Tumours of the Lung I.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. Maxwell P. Ellis: Ulcers of the Mouth and Pharynx.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 2 p.m., Mr. B. McN. Truscott: Carcinoma of the Female Breast. (2) 4 p.m., Dr. H. S. Banks: Question and Answer on Common Infectious Diseases.

●ROYAL FACULTY OF PHYSICIANS AND SURGEONS OF GLASGOW.—5 p.m., Dr. E. McC. McGirr: Radioactive Isotopes.

ROYAL MEDICAL SOCIETY, Edinburgh.—8 p.m., Dissertation by Mr. A. A. Russell: Medicine and Atomic Warfare.

ROYAL MICROSCOPICAL SOCIETY.—At King's College, Newcastle-upon-Tyne, 6 p.m., Dr. Geoffrey Bourne, D.Phil.: The Living Cell.

Saturday, January 29

●UNITED NATIONS STUDENT ASSOCIATION.—At London School of Hygiene and Tropical Medicine, 2 to 7 p.m., conference on World Health.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Lawler.—On January 6, 1955, to Sylvia D. Lawler, M.D., wife of L. I. Lawler, 34, Wolseley Road, London, N., a son—Anthony John.

Suchett-Kaye.—On December 29, 1954, to Dr. Beryl (formerly White), wife of A. I. Suchett-Kaye, M.D., M.R.C.P., a son—Richard St. John Clarence.

Tucker.—On January 5, 1955, at the Rubislaw Nursing Home, Aberdeen, to Helen (formerly Rennie), wife of Dr. Hugh M. Tucker, Urquhart Villa, Lossiemouth, Morayshire, a sister for Malcolm, Gillie, and Mandy—Sally Ann Richardson.

Warren Browne.—On January 8, 1955, at King's College Hospital, London, S.E., to Muriel, M.B., Ch.B. (formerly James), wife of Dr. D. Warren Browne, of Cowes, Isle of Wight, a daughter.

DEATHS

Devitt.—On December 26, 1954, at Hermanus, Natal, South Africa, Denis Christian Devitt, M.R.C.S., L.R.C.P., F.F.A. R.C.S., formerly of Northwood, and Ruislip, Middlesex, aged 48.

Any Questions ?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

How Much Sleep for Young Children ?

Q.—*I should like to know what is the consensus of medical opinion regarding the number of hours of sleep which a healthy, extremely active child of 3 years should have. Also, whether it is considered advisable that such a child should have a mid-day sleep or rest.*

A.—Perhaps more important than the consensus of medical opinion is the individuality of the child. Many notably active children are especially so at the age mentioned, thrive satisfactorily although sleeping less than might be expected, and by the time of their fourth birthday sleep heavily in the way characteristic of the older child. Allowing that individual requirements vary considerably, a child of 3 can be said to require about 12 hours' sleep in the 24 hours. A mid-day sleep is not essential and should not be insisted upon if it results in too little sleep or in prolonged delay in going to sleep at night. On the other hand, a mid-day *rest* is desirable, as the relaxation will conserve the physical reserves of the very active child.

Lack of Sexual Desire at Menopause

Q.—*I have a patient who is 45 years old, with five children. She is now at the menopause and has no desire for sexual intercourse. Could you advise an aphrodisiac drug which could be used with safety ?*

A.—Although it is natural for sex drive to weaken with advancing years, the menopause itself should not result in loss of desire *unless the woman concerned expects it to do so.* Many women tend to regard the change of life as the end of life so far as sex function is concerned, and it is this attitude rather than any hormone change which may cause frigidity. In fact, women with a proper outlook may continue to desire and enjoy coitus after the menopause ; some even go through a phase of increased desire. In the case cited there may be other factors concerned as well—fear of pregnancy, for example, which so many women experience as they approach the menopause. But, whatever form they take, the factors are likely to be psychological rather than endocrinological.

There are no aphrodisiac drugs of real value, and, even if it would help, oestrogen therapy is not indicated because of possible undesirable side-effects. It is claimed that androgens in small doses can increase libido in women, but the evidence is not very convincing, and inert tablets sometimes have an equally good effect.

Antibiotics in Tetanus

Q.—*What antibiotics are the best to use in the treatment of tetanus ? How effective are they ?*

A.—Two possible effects of antibiotics in tetanus must be distinguished, that on the primary disease and that on complications, particularly pneumonia.

Cl. tetani is moderately sensitive to penicillin (inhibited by about 0.1 unit/ml.), and an effect on the multiplication of this organism in the body can therefore be expected. Clinical evidence of the usefulness of penicillin in modifying the course of the disease is contradictory. Buxton and Kurman[1] used it as an adjuvant to treatment with antitoxin and sedatives in two cases ; Diaz-Rivera *et al.*[2] used it in 10 cases out of a series of 59 : in each of these papers it is concluded that penicillin is of value, but the findings have no statistical significance. Altemeier[3] used penicillin in 13 out of a series of 16 cases, and regarded it as of no value ; the dose used was small by present-day standards. Perhaps the main argument against the efficacy of antibiotics in tetanus is the fact that complete excision of the wound often fails to save life. If total removal of the focus of infection—often a simple procedure, since a small punctured wound is a frequent cause—is ineffective, what can be expected of chemotherapy ? It has to be concluded that toxin already formed and fixed in the central nervous system can cause death despite all measures to prevent its further formation.

The prevention of pneumonia is a legitimate indication for the use of antibiotics in tetanus, and penicillin is commonly used for this purpose. There is no information on which to decide whether any of the broad-spectrum antibiotics would be more effective. This aspect of the problem differs little from that of preventing autogenous descending infections of the bronchi and lungs under other circumstances.

REFERENCES
1 *J. Amer. med. Ass.*, 1945, **127**, 26.
2 Ibid., 1948, **138**, 191.
3 Ibid., 1946, **130**, 67.

Myokymia

Q.—*A man aged 43 years suffers from fibrillary movements all over the body. About nine months ago he had an attack of bacillary dysentery in South Africa, and the condition developed after that. He has been under my observation for the past five months, and the fibrillation appears spasmodically over the muscles of all four limbs, abdomen, and trunk, but no wasting has occurred. There is no loss of power, and both deep and superficial reflexes are normal. There is no pain, no loss of weight, or elevation of the temperature. What investigations are indicated ? What are the treatment and prognosis ?*

A.—Widespread fibrillation or fasciculation in the muscles may occur without atrophy in persons who are without other symptoms, though it is sometimes associated either with an abnormal liability to muscular cramp, increased sweating, or both. This condition, known as myokymia, is quite harmless. Though the fasciculation, resembling as it does that of motor neuron disease, may at first give rise to anxiety, there is no development of weakness, atrophy, or signs of pyramidal disease. Nothing is known of the cause of this form of myokymia, but the writer has seen it in one instance follow an attack of dysentery. The myokymia may persist indefinitely, but does not as a rule trouble the patient when anxiety has been relieved. There is no treatment known to the writer which is effective.

Transfusion in Head Injuries

Q.—*How should the principles of early transfusion in severe injuries be applied to the treatment of head injuries ? Is not the maintenance of a good blood supply to vital centres, depressed by both local trauma and systemic shock, more important than the traditionally taught danger of increasing intracranial haemorrhage by raising the blood pressure ?*

A.—If a patient who has sustained a head injury has also lost a quantity of blood from a wound elsewhere and shows clinical evidence of this blood loss, it should be made good by transfusion. Should raising of the blood pressure give rise to further intracranial bleeding this must be recognized and treated, as it should be had there been no indication for blood transfusion.

On the other hand, a head injury alone, without external bleeding, would provide no indication for a blood transfusion. The state of cerebral concussion which immediately follows a head injury is recovered from rapidly and spontaneously in the great majority of cases. The pallor, low blood pressure, and shallow respiration which characterize this state are therefore not to be regarded as evidence of surgical shock. In more severe head injuries with contusion and laceration of the brain the clinical picture is not one of shock, and the pulse is slow with the blood pressure often

elevated. Though in the most severe injuries with brain-stem haemorrhages the pulse and respirations will be rapid, there is nothing to indicate transfusion in therapy. Of essential importance in cases of brain injury is the avoidance of cerebral anoxia by maintaining a clear airway. This can usually be effected by gentle suction through the mouth, but when this is inadequate tracheotomy is a life-saving measure.

Inhalation Therapy

Q.—*What is the place of inhalations in modern therapy?*

A.—The use of inhalations in modern therapy is very limited. Apart from the volatile anaesthetics, inhalations for nasal catarrh, and amyl and octyl nitrite, certain non-volatile substances can be thus administered. They may be in solution as adrenaline for asthma, or in fine suspension as penicillin for certain respiratory infections, although the employment of penicillin in this way is on the wane.

Although a great variety of drugs could be given by inhalation, there is no special virtue in this route apart from the rapid effect due to quick absorption. The amount absorbed cannot be controlled with any accuracy, and a danger of local irritation, as from the stramonium fumes of asthma cigarettes, must be borne in mind.

Aphthous Ulcers

Q.—*A girl of 7 has for several years suffered from small painful ulcers of the mouth. Otherwise she is quite fit. She is about to start orthodontic treatment, and her dental surgeon insists that the ulcers should be dealt with before appliances are fitted. Can you suggest any investigations and treatment that may be profitably carried out? Vitamins A and B have been given and alkaline mouth-washes, with no improvement.*

A.—Unfortunately the aetiology of aphthous or so-called dyspeptic ulcers still remains obscure in spite of the considerable amount of work done on the subject. They are now in fact thought to have no connexion with dyspepsia and are seen more frequently in females than in males. The ulcers are formed as a result of the breaking down of vesicles resulting from intra-epithelial oedema of the stratum granulosum of the oral mucosa.

Local antibiotics have been tried and some success has been claimed, but they are unlikely to prevent the formation of vesicles, although they may diminish the secondary infection when the vesicles break down. There is some evidence that the ulcers may be allergic in origin, and on this basis antihistaminics have been employed and success has again been reported. The formation of vesicles has also suggested the possibility of virus infection, and on this basis virus vaccines have been employed; again a small amount of success has been claimed. Vitamins A, B, and C have all had their adherents, but no sustained success has been reported. Local demulcent mouth-washes are of value, but the treatment often advocated—of painting the ulcers with a caustic—cannot be recommended, since this usually merely prolongs the healing process and does not prevent the formation of further ulcers.

NOTES AND COMMENTS

Home-made Anti-freeze.—Dr. G. W. FLEMING (Gosport, Hants) writes: Referring to the answer given to this question ("Any Questions?" December 11, 1954, p. 1434), what is wrong with industrial methylated spirit? I have used it for 40 years with complete success in a ratio of 1 to 7 parts of water. Have I just been lucky, and is not this mixture as reliable as I think it is? It is certainly cheap (3s. to 4s.) compared with other anti-freeze mixtures. It could boil off, I suppose, but I just keep my radiator topped up with 1 in 7 methylated spirit and water and have never had a freeze-up. I put an old Army blanket over my radiator at night as well, but my garage is unheated and without doors—just an open shed.

Dr. W. H. DICKINSON PRIEST (London, W.1) writes: I was more than somewhat shaken by your expert's statement that glycerin has a corrosive action, especially as I was just about to treat my car to its annual dose of one part in sixteeen, as I have done all my motoring life with nearly all my other cars. With great respect, may one inquire the basis for this statement? That it (and proprietaries) stir and scour up rusty sludge is admitted, but is not this a good thing for the next drain-out? If the proprietaries contained an anti-rust chemical, which I believe is general now in the U.S.A., one would not resent their expense so much, but so far as I know this has not reached this country yet. I am not aware of having suffered any ill effects ever from glycerin. I may add that I have asked several garage proprietors with whom I deal and they profess ignorance of the alleged corrosive action. I would be grateful for further information.

OUR EXPERT writes: The general position regarding the anti-freezes for car cooling systems can be briefly summarized as follows: There are a number of substances which, when added to the cooling water in the radiator, lower its freezing point sufficiently to prevent it from freezing in winter, without at the same time reducing the cooling capacity of the system. Unless inhibited by means of appropriate additives, however, every one of these anti-freeze solutions causes corrosion of the cooling system components, the intensity of attack depending to a large extent not only on the anti-freeze used but also on the combinations of metals found in the particular cooling system, type of car operation, etc. With ethylene glycol, methanol, and ethanol (as well as methylated spirit), which form the basis of most commercial anti-freezes, this attack is usually relatively mild, its intensity being of the order of that of ordinary water. The addition of special corrosion inhibitors greatly reduces this attack. It should perhaps be stressed at this point that such bodies as the Society of Automotive Engineers in America and the U.S. National Bureau of Standards consider the corrosive action of ordinary water in the radiator excessive for satisfactory operation of the cooling system, and recommend the use of corrosive inhibitors in cooling *water* in summer. With uninhibited glycol or alcohol in the radiator, it is improbable that any serious defects in the cooling system would become obvious in the first two or three years of operation, and, under favourable conditions, perhaps during the whole life of the car. The corrosive action of glycerin has been reported by the U.S. National Bureau of Standards in its Circular No. 506 of November, 1952. Also, the Swiss Society for the Study of Motor Fuels at Berne observed that the attack by glycerin, while generally low, assumed the particularly dangerous form of localized pitting of iron and solder metal. The composition of proprietary anti-freezes is not normally disclosed by the makers, but there is no doubt that most, if not all, of them do in fact contain corrosion inhibitors. In the formula recommended by the Chemical Research Laboratory, quoted in the *British Medical Journal* of December 11, 1954 (p. 1434), sodium benzoate and sodium nitrite perform this function. Finally, I should like to draw Dr. Dickinson Priest's attention to the fact that his one-in-sixteen solution of glycerin protects his cooling system against only 2 to 3° F. (1.1 to 1.7° C.) of frost. A one-in-seven solution of methylated spirit and the anti-freeze of the Chemical Research Laboratory give protection against about 7 and about 18° F. (3.9 and 10° C.) of frost respectively.

Skin Ink.—Dr. N. S. FINZI (Cobham, Surrey) writes: As the originator of the formula[1] given in reply to a question on skin ink ("Any Questions?" January 1, p. 55) I should like to add a few words of advice as to its use. It oxidizes readily and is then of no use for skin marking. To avoid this it should be made up in small quantities only, in small well-corked or stoppered bottles. In order to diminish the rate of oxidation, I use 0.2 ml. of sulphurous acid instead of the hydrochloric acid. It is not permissible to use it in radiotherapy patients in any part exposed to radiations, on account of secondary radiation from the iron: a solution of fuchsin is used for these, but it is not so permanent, if washed.

REFERENCE

[1] *British Medical Journal*, 1918, 1, 52.

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